The influence of social contact on risk of dementia

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Declaration

I, Andrew Sommerlad, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Andrew Sommerlad Date

Acknowledgements

I would like to thank my supervisors, Gill Livingston, Glyn Lewis and Archana Singh-Manoux for their incredible encouragement and guidance during the course of applying for funding and undertaking this PhD. Gill's academic and pastoral support has been exceptional over the past six years, enabling me to get to this point and continuing to inspire me to try to improve the lives of people living with dementia.

I am thankful for the help I received from Séverine Sabia, Joshua Ruegger, Gayan Perera, Christoph Mueller, Hitesh Shetty and Rob Stewart in conducting my research and writing up my PhD findings for publication, and to my friends and colleagues at UCL for their support throughout. In addition, I would like to give thanks to the Wellcome Trust for funding me during this PhD.

Finally, my family have given unstinting support throughout my struggles and successes, so I am immensely grateful to Mary, Mum and Dad for helping me to persevere, and to Tom for reminding me what is most important.

Abstract

Background: There is need for identification of modifiable risk factors for dementia as intervention targets. Social network contact may reduce dementia risk through building cognitive reserve, but previous observational study findings are susceptible to reverse causation bias due to short follow-up.

Aim: To examine the influence of social contact on incident dementia.

Methods: I conducted a systematic review and meta-analysis of the association of marital status, used as a proxy measure for cumulative lifetime social contact, and dementia. I next examined the accuracy of English routinely-collected hospital data on dementia diagnosis to establish the validity of using these records to ascertain dementia status. I then used the Whitehall II prospective cohort study to examine the association of social contact frequency and incident dementia, ascertained from routinely-collected databases.

Results: The pooled relative risk of dementia for people who were single or widowed, compared to married, was 1.42 (1.07, 1.90) and 1.20 (1.02, 1.41) respectively, an association which persisted after adjustment for potential confounding variables.

I found that routinely collected hospital data included, during 2.5 mean years of follow-up, records of dementia for 78% of people with "gold-standard" dementia diagnosis; diagnostic recording was less likely for single people than married (odds ratio = 0.81 (0.67, 0.99).

I found that more frequent social contact at age 60 years was associated with lower risk of dementia (hazard ratio = 0.88 (0.79, 0.98)) but risk for social contact at 50 or 70 years was similar but not significantly associated. More frequent social contact during mid-life was associated with higher baseline cognition, but not subsequent rate of cognitive decline.

Conclusions: More frequent social contact is likely to be associated with lower risk of subsequent dementia. This may be because social contact builds greater cognitive reserve, thereby delaying dementia onset, or that social contact is a marker of those with higher cognitive reserve.

Impact statement

The work included in this PhD thesis has potential to impact: 1) the general population including people with dementia, 2) those implementing health and social care policy, and 3) the academic community.

Association of dementia with social contact and marital status

1. *Patient and public impact*

The findings that social contact and marital status is associated with dementia risk has strengthened the evidence base suggesting social contact is a potentially modifiable risk factor for dementia. Awareness of this link has the potential to affect some older people directly, by encouraging behavioural modification to increase social contact, or through future development and implementation of public health or clinical interventions to increase social contact.

I disseminated information on the links between marital status and dementia and the potentially modifiable mechanisms to a wide audience through various avenues. I was interviewed by newspaper journalists from the UK, Canada, US and Australia; interviewed on television (BBC World) and radio; discussed my findings in a podcast; and spoke at a University of Cambridge public engagement debate.

2. *Public health and policy impact*

My findings on the increased risk of dementia associated with low social contact have the potential to have impact on public health policy. In the UK, Public Health England have made recommendations on how to reduce dementia risk, which include encouraging people to 'connect with people' and community-level public health recommendations of 'interventions to address healthy lifestyles [and] social isolation' (Public Health England, 2018). Furthermore, the World Health Organisation are currently producing evidence-based standard guidelines about dementia risk reduction and I have been invited to review these guidelines. My findings may

support the implementation of community-level measures to increase social contact in the general population.

3. Academic impact

My findings are applicable to academics in psychiatry, psychology, medicine, nursing and sociology. I have published my meta-analysis and presented findings at national and international conferences. I intend to publish and present my findings on social contact and dementia. Future research may examine the replicability and potential mechanisms of my findings. My results also support the development of interventions and testing of their feasibility and efficacy.

Accuracy of dementia diagnosis in general hospitals

My findings have the potential to inform diagnostic practice in general hospitals as they identified rates and predictors of missed dementia diagnosis in English general hospital records. Measures to improve identification and recording of diagnosis in hospital may benefit people with dementia and their families. My study was discussed in the media and I was interviewed on national television (Sky News) and radio (LBC) about my findings. This research may guide improved training for hospital clinicians in dementia detection and suggests need for improved sharing of diagnostic information between health care providers, such as through automatic population of hospital records with known conditions, to increase clinician awareness of comorbidities including dementia. My findings also clarify the validity of Hospital Episode Statistics as a tool for epidemiological and clinical research, so will be of use to other researchers intending to use this data-source.

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Statement of personal contributions

I wrote the funding application and was awarded a Wellcome Trust Research Training Fellowship to undertake the work included in this thesis. I conducted the literature searches, screening of abstracts, data extraction, quality rating, meta-analyses and narrative synthesis of results for the systematic review.

I cleaned and conducted all analyses of the data for the observational study on the validity of hospital diagnoses of dementia.

I cleaned and conducted all analyses of the Whitehall II study data for the observational study of social engagement and dementia.

I wrote all of the thesis content.

List of abbreviations

CI – Confidence interval

CRIS – Clinical record interactive search

GATE – General architecture for text engineering

HR – Hazard ratio

HES – Hospital episode statistics

HoNOS – Health of the nation outcome scale

ICC – Intraclass correlation coefficient

ICD-10 – International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

IMD – Index of multiple deprivation

IQR – Interquartile range

IRR – Incidence rate ratio

MBI – Mild behavioural impairment

MCI – Mild cognitive impairment

MMSE – Mini-mental state examination

NICE – The National Institute for Health and Care Excellence

NHS – National Health Service

OR – Odds ratio

PPV – Positive predictive value

RR – Relative risk

SD – Standard deviation

Chapter 1: **Introduction**

While undertaking my master's degree in psychiatric research, I conducted qualitative interviews with people with dementia and family carers to understand the changes in social functioning which occur in dementia (Sommerlad et al., 2017). People with dementia and their family members revealed some of the distressing changes which they had noted during the course of the dementing illness. One husband said that his wife had lost her emotional sensitivity since developing dementia: '*she never says, "are you alright darling?" anymore*'. A wife of a man with dementia told me that conversation with her husband had diminished over time: '*He just gives very short answers, like he wants the conversation to finish'.*

Other interviewees hinted that these difficulties in social functioning, known and described in the later stages of dementia, had predated the diagnosis and therefore may be a sign of the developing illness. One patient, a retired GP, said that in the years leading up to his dementia diagnosis, he had struggled to keep track of conversations with his group of friends: '*it made my conversation with other people get less and less. You know, because I couldn't talk about things with them ... if I saw somebody I knew, I didn't think that I'd be able to discuss with them".*

A number of previous studies have reported that having infrequent social contact is associated with increased risk of cognitive decline and dementia. However, the experience of the people living with dementia who participated in my research suggested to me that this lack of social contact may be an early feature of dementia, rather than solely be a risk factor for the condition. In this PhD I intend to clarify, through systematic review and analysing data from the Whitehall II longitudinal cohort study where people are followed up over decades, whether social contact has an influence on risk of cognitive decline and dementia, whether such findings are features of early disease due to reverse causation, or both.

1.1 Scope of PhD thesis

In chapter 2, I will define dementia and social network contact and summarise the background to this thesis. I will discuss evidence from the literature about the association between social contact and subsequent risk of developing cognitive decline and dementia, as well as the social changes seen in established dementia and consider possible mechanisms for these associations.

In chapter 3, I will outline the aims and objectives of the research I undertook in my subsequent studies.

In chapter 4, I will describe the systematic review and meta-analysis that I conducted of the association between marital status and dementia risk. I chose to examine marital status as recent systematic reviews had examined the association of social engagement and dementia (Kuiper et al., 2015) and cognitive impairment (Kuiper et al., 2016). However, studies included in these reviews were susceptible to reverse causation bias because of the short time period between measurement of social engagement and the outcome, meaning that low social engagement could have been an early consequence of dementia, rather than a cause (described in more detail in section 2.3.2). I viewed marital status as a surrogate measure of lifetime cumulative social contact; as married people usually live together with their spouse and have more frequent social contact than those who are single or widowed (Campbell and Lee, 1992). I also considered marital status is less likely to be affected by reverse causation, as marriage usually occurs many decades before the development of dementia and marital status is unlikely to change as a result of early dementia. This study was published in *Journal of Neurology, Neurosurgery and Psychiatry* in November 2017 (Sommerlad et al., 2018b) (Appendix 1).

In chapter 5, I will describe a cohort study examining the validity of NHS routinely collected dementia diagnoses from general hospitals, the Hospital Episode Statistics (HES) database. I conducted this study as I intended to use HES data to ascertain dementia status in my subsequent work, as the Whitehall II study is electronically

linked to HES data, as well as other data-sources. However, there are concerns as to the accuracy of using electronic register data such as this for the diagnosis of dementia, considering that not all people with dementia access health services and their dementia may not be recognised or recorded. I have therefore used a large cohort of older people derived from specialist mental health care services as a gold standard against which to calculate the sensitivity and specificity of HES dementia records. I have written two manuscripts reporting these studies; the first was published in *Alzheimer's and Dementia* in July 2018 (Sommerlad et al., 2018a) (Appendix 5), and the second was published in *European Journal of Epidemiology* in January 2019 (Sommerlad et al., 2019) (Appendix 8). This study indicated that use of HES to ascertain dementia status for my subsequent research would be acceptable but that results should be interpreted with consideration of the potential for measurement bias.

In chapter 6, I will describe my observational cohort study using the Whitehall II study to examine the association between frequency of social network contact and both cognitive decline and dementia. I used data from this cohort to examine my hypothesis that higher level of social contact during mid- to late-life is associated with reduced risk of developing dementia because 1) Whitehall II has examined social contact at age 35 to 55, at a time when prodromal symptoms of dementia are unlikely to be present thereby reducing risk of reverse causation bias, and 2) measurements have been taken at six separate occasions over 25 years, allowing examination of associations of dementia with social contact at different ages.

In chapter 7, I will summarise and discuss the overall conclusions of my thesis and future work arising from my findings.

Chapter 2: **Background**

2.1 Dementia

Dementia is an acquired clinical syndrome of impairment of multiple cognitive functions such as memory, language, orientation and calculation, with consequent impairment of functional ability (World Health Organisation, 2004). There are a range of neuropathological causes of dementia with the commonest being Alzheimer's disease, which accounts for around two-thirds of cases, and other common causes being vascular dementia, Lewy body dementia and the fronto-temporal dementias (Prince et al., 2014). There are around 850,000 people in the UK and 50 million worldwide who have dementia.

Life expectancy has increased markedly over the past 60 years, from 66.4 years for UK men and 71.5 years for UK women in 1951, to 79.2 and 82.9 years respectively in 2011 (Office for National Statistics, 2018). Life expectancy increases globally have been attributed to healthier lifestyles including reduced smoking rates and lower cardiovascular mortality (Mathers et al., 2015). Dementia incidence is strongly age-related (Hofman et al., 1991), with incidence approximately doubling for every five year increase in age (Jorm and Jolley, 1998) meaning that the number of people who have dementia is rising in the UK (Ahmadi-Abhari et al., 2017). This increase is amplified globally, where similar demographic changes are occurring at a faster rate; the number of people with dementia is projected to rise from 10.5 million in Europe in 2015 to 18.7 in 2050 (a 78% rise), and from 46.8 million globally in 2015 to 131.5 in 2050 (a 181% rise) (Prince et al., 2015).

2.1.1 Risk factors for dementia throughout the life-course

As well as age being a risk factor for dementia, several health conditions and lifestyle factors have been found to be associated with all-cause dementia, as summarised in the 2017 Lancet Commission for Dementia Prevention, Intervention and Care, to which I contributed while undertaking my PhD (Livingston et al., 2017). There is some

genetic vulnerability to dementia; in over-65s, the apolipoprotein E (ApoE) ε4 allele confers the largest genetic risk (Brouwers et al., 2008, Corder et al., 1993), although the relative contribution of ApoE profile to dementia incidence, calculated by population attributable risk, is low at an estimated 7% (Ritchie et al., 2010). In young-onset dementia the genetic risk profile is different, with genetic contribution to aetiology thought to be higher (Rossor et al., 2010) and some rare specific gene mutations associated with very high dementia risk (Chen and Schubert, 2002), although lifestyle factors are also important (Nordström et al., 2013).

Health behaviours and conditions related to cardiovascular and cerebrovascular health – diabetes, hypertension, obesity, physical inactivity – increase dementia risk (Norton et al., 2014, Whitmer et al., 2005). High intelligence (Larsson et al., 2017) and higher levels of education in childhood (Meng and D'Arcy, 2012) are consistently associated with lower risk of dementia. Continued learning in later life through employment or learning new skills (Valenzuela et al., 2011, Lee et al., 2018) may also reduce dementia risk and recent evidence suggests that peripheral hearing loss may also affect dementia risk (Wei et al., 2017). These are likely to act by building cognitive reserve (Stern, 2012, Valenzuela and Sachdev, 2006), which I will describe in more detail in section 2.1.1.1.

2.1.1.1 Cognitive reserve

The concept of cognitive reserve describes individuals' ability to tolerate more neuropathology without cognitive and functional decline, related to either the brain anatomical substrate or adaptability of cognition. Interest in this concept first emerged during the late 1980s, when a post-mortem study indicated discrepancies between the degree of cerebral Alzheimer's disease pathology and cognitive impairment, leading the authors to speculate that the subgroup with pathological changes but no symptoms may have had greater reserve as a result of having larger brains or more dense neuronal structure (Katzman et al., 1988).

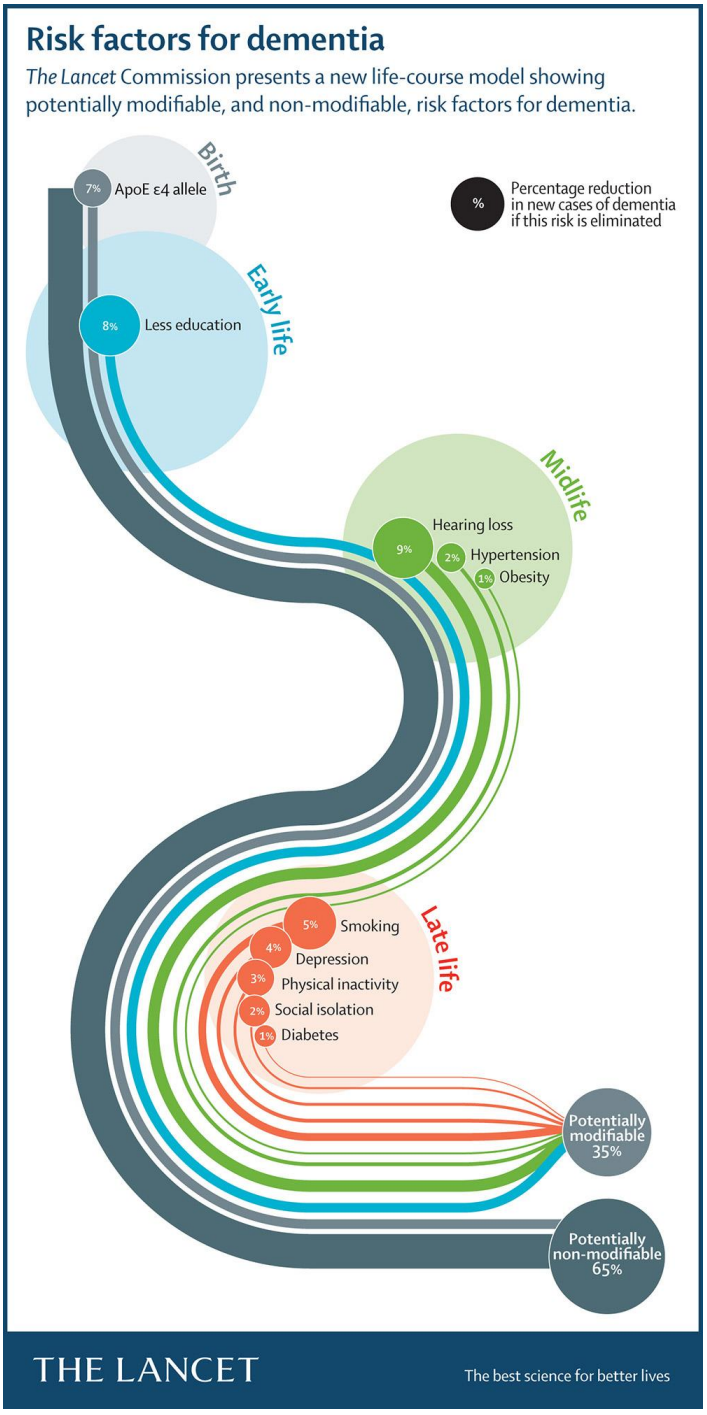
Subsequent studies have indicated that factors which are considered to be proxies for greater cognitive reserve are associated with lower risk of clinical symptoms of

dementia for a given level of neuropathology (Richards and Deary, 2014, Snowdon et al., 1996). No single domain can exactly reflect cognitive reserve, but the most commonly used proxy for estimating reserve has been the level of educational (Stern, 2012) or occupational attainment (Rusmaully et al., 2017), and other factors such as height, which may reflect early social and material environment, have also been used to estimate cognitive reserve (Rusmaully et al., 2017, Singh-Manoux et al., 2011). I will outline the relevance of cognitive reserve in the potential association between social contact and dementia in more detail in section 2.3.1.

2.1.2 Life-course model of dementia risk

Dementia risk may therefore be a dynamic process throughout the life-course. The lifelong development of cognitive reserve (Richards and Deary, 2005), through high intelligence and participation in education and other cognitively-stimulating activities, protects against the deleterious effect of neuropathological change, and thereby delays progression to dementia diagnostic threshold. It is hypothesised that risk factors may be more important at some points in life than at others, so studying risk factors throughout the life-course (Larson, 2018) and targeting interventions at the appropriate age-groups is likely to be important (Kivipelto et al., 2018). Figure 2-1 shows a summary of the risk factors currently proposed in US and UK national guidelines (Daviglus et al., 2010, National Institute for Health and Care Excellence, 2015), their contribution to dementia incidence estimated by population attributable fraction, and the age-group at which association with dementia has been found, from the Lancet Commission report (Livingston et al., 2017).

Figure 2-1: Life-course model of contribution of modifiable risk factors to dementia



Notes: Reproduced from (Livingston et al., 2017) by permission of The Lancet.

2.1.2.1 All-cause dementia and dementia subtypes

The specific dementia syndromes of Alzheimer's disease and vascular dementia share many risk factors. Obesity, elevated cholesterol, and hypertension, usually considered to be vascular risk factors, increase risk of Alzheimer's disease (Kivipelto et al., 2005), and these may act through oxidative stress and inflammation increasing amyloid beta deposition, the pathological hallmark of Alzheimer's disease (Casserly and Topol, 2004), or impaired insulin receptor activation, which is also seen in Alzheimer's disease (Frölich et al., 1998). Pathology in dementia in older people is usually mixed (Rahimi and Kovacs, 2014) and accurate diagnosis of specific dementia subtypes can be difficult in routine clinical settings meaning that misclassification is common (Boiler et al., 1989). Furthermore, in clinical practice, many people do not undergo investigations usually necessary to differentiate dementia subtype, so are diagnosed with unspecified dementia (Gomm et al., 2016, Adelborg et al., 2017). For these reasons, my primary aims of this thesis refer to all-cause dementia, rather than examining dementia subtypes, as I also discuss in section 6.2.2.2.

2.1.3 Changing rates of dementia

There is evidence that dementia prevalence rates are changing in some countries, with reduced prevalence and incidence rates over the past 15-20 years reported in the United Kingdom (UK) (Matthews et al., 2013, Matthews et al., 2016), the United States (US) (Satizabal et al., 2016, Langa et al., 2016), the Netherlands (Schrijvers et al., 2012) and elsewhere (Roehr et al., 2018, Wu et al., 2017). In the UK, the CFAS study reported prevalence rate in 2008 to be 0.7 times (95% confidence interval (CI) 0.6, 0.9) that of 1991 (Matthews et al., 2013). A meta-analysis of findings of five comparable studies in the USA, UK, France, Netherlands and Japan found incidence rate to be 0.82 time lower (0.51, 1.33) in follow-up cohorts compared to original cohorts, a mean of 12.6 years later (Roehr et al., 2018). Incidence rates in China (Chan et al., 2013) and prevalence rates in Japan (Ohara et al., 2017) have, by contrast, been reported to have increased during the past 20 years.

The changing incidence and prevalence rates in successive cohorts of older people has been attributed to population level changes in risk factors conferring protection

against dementia. Evidence for this phenomenon is limited, as deductions from observed changes in risk factors at population levels are susceptible to ecological fallacy (Piantadosi et al., 1988). However, the decline in prevalence of dementia in the US Health and Retirement Study was associated with increased levels of education (Langa et al., 2016). It was also possibly related to improved and earlier treatment of cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia; better cardio- and cerebrovascular health associated with lower dementia rates was identified in the Framingham Study, which found the reduction in risk was observed only among persons who had at least a high school diploma education (Satizabal et al., 2016).

2.1.4 Social contact as a dementia risk factor

In this thesis, I aim to examine whether frequency of social contact influences the risk of developing cognitive decline and dementia. Previous studies have found more social contact to be associated with lower rates of dementia (Kuiper et al., 2015) and cognitive decline (Kuiper et al., 2016) at follow-up. However, most previous studies have had only short duration of follow-up after social contact assessment, meaning that they are susceptible to reverse causation, whereby declining social contact in the prodromal phases of dementia results in a spurious association being found. Pathological changes (Jack et al., 2010) and symptoms (Amieva et al., 2008) of dementia have been identified at least 2-3 years before diagnostic threshold is reached, and limitations in social functioning are characteristic of dementia (World Health Organisation, 2004), therefore it is plausible that social changes are an early consequence of, rather than risk factor for, dementia. I will discuss the evidence of the association of social contact and both dementia and cognitive decline in more detail in section 2.3.

2.1.4.1 Possible research and clinical implications

Examining whether social contact influences dementia risk has important potential clinical and research implications. Dementia prevention is a key public health priority (Pickett et al., 2018), so if social contact confers protection against dementia, then social contact may be a modifiable risk factor which could be targeted in future

studies aiming to prevent or delay dementia. There has been a trend over time toward the amount of direct social interactions decreasing; between 1985 and 2004 in the US, the number of people reporting having no confidant tripled (McPherson et al., 2006) and this may be a particular problem for older people, who report less social contact than younger people (Davidson and Rossall, 2014). There is increasing interest in the potential of social interventions to improve social connectivity (Mann et al., 2017). Therefore, clarifying the association between social contact and dementia and cognitive decline, including identifying which aspects of social contact are important, may inform future development and implementation of tailored interventions.

If previous findings were simply related to reverse causation, and level of social contact is not a risk factor for dementia, then understanding the timing and nature of social engagement changes which result from dementia prodrome may permit earlier dementia detection, or differentiation of those who are likely to develop dementia from those with a better prognosis. Clinicians diagnose dementia when functional changes accompany cognitive decline (World Health Organisation, 2004, American Psychiatric Association, 2000). Typically in clinical practice, functional impairment is considered by enquiring about difficulty in an individual's ability to carry out activities of daily living such as maintaining personal care (washing and dressing), managing household duties (cleaning and cooking) and finances, and navigating using personal or public transport. However, if decline in social contact precedes dementia, then clinicians should enquire about the presence of these symptoms early in clinical assessment.

Identification of social changes preceding dementia in a large cohort study may also help patients and their friends and families to understand that subtle social behavioural changes may be a consequence of dementia rather than being an active choice of a person with dementia, which is a frequent misconception which can impair relationships (Singleton et al., 2017). Previous psychosocial interventions with family carers of people with dementia aimed at understanding dementia related problems, improving coping skills, and addressing problematic behaviours have

yielded benefits for carers (Livingston et al., 2014) and people with dementia (Spijker et al., 2008). Therefore, were I to find that reduced social contact is a prodromal feature of dementia, it may be that addressing social changes would be beneficial for people affected by dementia.

2.2 Social contact

Desire for social relationships is considered to be an inherent aspect of human nature which may have neurobiological underpinnings (Young, 2008), and social contact with other people is a core part of individual identity (Watts et al., 2002) and important for wider society.

2.2.1 Defining social contact and differentiation from other concepts

In this thesis, I will use a classification of social contact which is frequently used in research literature (Kuiper et al., 2015), as referring to visiting or communicating with relatives, friends and acquaintances. Social contact frequency is one aspect of social relationships, which 'exist between two people when each person influences the other's thoughts, feelings, and/or behaviour, i.e. when people are at least minimally interdependent' (Smelser and Baltes, 2001) and there are many other concepts linked to social relationships which have received interest in previous research. I define these, and how they differ from social contact, in Figure 2-2.

Figure 2-2: Concepts in social relationships

Social contact	A quantitative measure relating to visiting or communicating with relatives, friends, and acquaintances, usually but not necessarily as a recreational activity; and not encompassing qualitative aspects of satisfaction with social contact.
Social engagement	Participation of an individual in a range of social roles and relationships, usually referring to both social contact and participation in social and community activities (Avison et al., 2007).
Loneliness	A subjective unpleasant experience that occurs when a person's network of social relationships is significantly deficient in quality (Perlman and Peplau, 1984).
Social isolation	The inadequate quality and quantity of social relations with other people at different levels of human interaction (individual, group, community and the larger social environment) (Zavaleta et al., 2014).
Social network	A sociological concept relating to linkages among a defined set of persons; the characteristics of these linkages as a whole may be used to interpret the social behaviour of the persons involved (Thompson, 1973).
Perceived social support	Beliefs about the quantity and quality of support that is potentially available from the individual's relationships and social contacts (Stringhini et al., 2012).

Components of social relationships can be divided into 'structural', which relate to the amount of participation in social relationships e.g. social contact, social engagement, social isolation, marital status or living alone v cohabiting; and

'functional', which refers to satisfaction with social relationships, e.g. loneliness, perceived social support. Structural and functional measures of social contact are only weakly correlated (Lakey and Cohen, 2000); that one can 'feel lonely in a crowd' is often acknowledged. In one study, the correlation between structural and functional (or received and perceived, as the authors described these concepts in this study) instrumental support in one study was r = 0.25, and 0.19 for the correlation between perceived and received affective support (Reinhardt et al., 2006). However, both structural and functional aspects of social relationships have been found to be associated with health outcomes (Holt-Lunstad et al., 2015, Holt-Lunstad et al., 2010).

2.2.2 Measuring social contact

For measurement of social contact to be relevant to long-term health effects, they need to quantify individuals' social contact over a prolonged period of time, as patterns of social contact have considerable variation (Cornwell, 2011), such as throughout the course of a day or between different days of the week, related to the structure of a working week (Mossong et al., 2008). Objective *in vivo* measurement of social contact over extended periods of time, by observing the frequency of a person's contact with others, is unfeasible and so measurement of social contact has usually relied upon self-report by a study participant or informant. This introduces risk of measurement error (Hutcheon et al., 2010) and potential for bias in observational studies. There is emerging interest in technological approaches to measuring social contact which might more objectively assess social contact frequency. For example, it is possible to examine mobile phone data for frequency and duration of telephone conversations (Matic et al., 2012) and use wireless sensors to examine proximity to others (Leecaster et al., 2016), but use of such technologies is in early stages in research settings, and longitudinal data is lacking.

There is inconsistent use of terminology in previous research examining aspects of social relationships and this may be partly due to limitations in tools to measure these domains, making it difficult to define what is being measured. Although some measures are in common use, such as the UCLA loneliness scale (Russell et al., 1980)

and the Lubben social network scale (Lubben, 1988) many studies have created their own scales (Mitchell et al., 2003), meaning that there are a range of different scales in use. This makes it difficult to compare studies, possibly contributing to variation in results of studies examining the health effects of social relationships.

Scales used have combined structural and functional aspects of social relationships, such as the Lubben Social Network Scale (Lubben, 1988) which asks respondents how many relatives they see at least monthly and how often they have contact with their closest relative (structural measures) and also asks about availability of relatives with which the respondent could talk about private matters or availability of relatives when an important decision needs to be made (functional). Other studies have used composite measures of social engagement, such as those which combine social contact and participation in social activities (Glass et al., 2006), or combined these with other concepts such as contact with work colleagues (Saczynski et al., 2006). This makes it difficult to determine which particular aspects of relationships have important health effects.

A recent systematic review (Valtorta et al., 2016) examined measures of social relationships which are in frequent use in research settings and proposed a classification system for these based upon two related dimensions. Scales were rated on 1) the extent to which they measured structural or functional aspects of social relationships, and 2) the degree of subjectivity asked of respondents, on a scale from asking respondents the size of their social networks and involvement in them, to perceived availability, adequacy, and to their feelings related to their relationships such as loneliness. Using this framework, the aforementioned UCLA loneliness scale (Russell et al., 1980) is rated as a measure of relationship function which examines subjective perceived adequacy and feelings related to personal relationships; the ENRICHD social support inventory (Mitchell et al., 2003) measures both relationship structure and function, asking participants about perceived adequacy and perceived availability of relationships; while the Lubben social network scale (Lubben, 1988) also measures structure and function of relationships, asking about involvement in relationships as well as their perceived availability.

2.2.2.1 Social contact frequency

In this thesis, I have chosen to examine social contact frequency, which is a largely objective measure of relationship structure, as I describe in more detail in section 6.1. Three scales were noted in the previous systematic review of social relationship measures (Valtorta et al., 2016) to measure solely structural aspects of relationships and to ask participants objective questions about their involvement in relationships. The Wenger support network typology (Wenger, 1991) and the Litwin support network type (Litwin, 1997) both aim to characterise individuals' social contact into network clusters relating to the groups with which the respondent has predominant social contact, e.g. 'diversified support networks' encompassing contact with friends and families, or 'family-focused networks'. The third scale judged as measuring structural aspects of relationships is the Berkman-Syme social network inventory (Berkman and Syme, 1979). This scale is a composite measure of marital status, social contact, and wider social engagement, e.g. church or community organisations, which aims to rate level of social contact from socially isolated to socially integrated. A modified version of the Berkman-Syme social network inventory, comprising only of the questions related to social contact has been administered on repeated occasions by the Whitehall II study (Marmot and Brunner, 2005) which I will use for my research reported in chapter 6.

2.2.3 Association of social contact and general health

In this section, I will briefly describe previous findings on the association between social contact and general health, including mortality, to place in a wider context my work on social contact's effects on cognition and dementia, and introduce some potential mechanisms; social contact may affect the body as well as the mind. Most previous research into the long-term health effects of social contact in humans has been observational (PLoS Medicine Editors, 2010), as any intervention which modifies individuals' social contact for prolonged periods of time is likely to be impractical and potentially unethical. Some studies have however examined the short- and medium-term effects of brief social interventions on human health, and studies in animals

have examined the effect of chronic isolation from social contact in monkeys (Harlow et al., 1965) and rats (Wilkinson et al., 1994).

Low level of social contact was found to be associated with elevated risk of mortality in a meta-analysis of 63 studies of humans examining the association between structural aspects of social relationships and mortality risk (Holt-Lunstad et al., 2010). Across these studies, the relative risk of death was 1.57 for study participants with lower structural social relationships; the largest effect was seen in studies using composite measures of social relations, such as marital status, social networks and social integration. These associations are strong in unadjusted analyses (Berkman and Syme, 1979) but also persist following adjustment for potential confounding variables, such as age, gender, physical illness and functional ability (Kiely et al., 2000). It is hypothesised that social contact may improve health by encouraging healthier behaviours such as reducing alcohol consumption, taking exercise and healthier diet (Pieper et al., 1989) or through stress reduction, by providing psychological and material resources needed to cope with stress (Cohen, 2004).

Specific effects on physical and mental health related to social contact have also been reported. Having large and diverse social networks was found in nine of 13 studies included in a systematic review to be associated with reduced risk of depression (Santini et al., 2015). Structural and functional aspects of social relationships predict coronary heart disease outcomes, with most studies in a systematic review finding association with both incidence and prognosis (Hemingway and Marmot, 1999).

Although some personality characteristics such as introversion (Leary et al., 2003), neurodevelopmental disorders such as autism (Chevallier et al., 2012) or internalised stigma as a consequence of mental health problems (Livingston and Boyd, 2010) may encourage some to seek and prefer solitude, social contact with others is usually associated with positive affective experience. More social network contact is associated with better life satisfaction in people with chronic illnesses (Jang et al., 2004) and social isolation is associated with the subjective experience of loneliness (Dahlberg and McKee, 2014).

2.3 Association of social contact with dementia and cognitive decline

Evidence from previous observational studies indicates that higher frequency of social contact is associated with reduced risk of subsequent cognitive decline and dementia. A 2015 meta-analysis summarised the evidence from longitudinal studies examining the association between a range of social relationship domains and dementia and found greater risk of dementia in those with less frequent social contact (Kuiper et al., 2015). In this study, the authors grouped together a range of different measures of social contact frequency (e.g. never visiting relatives vs visiting them at least weekly-monthly (Chen et al., 2011); having no contact with relatives or friends vs daily contact (Fratiglioni et al., 2000); or not participating in family activities vs participating (Gureje et al., 2011)). The duration of follow-up from assessment of social contact to assessment for dementia was between 2 and 15 years. The pooled relative risk from eight studies of dementia at follow-up was 1.57 (95% CI 1.32, 1.85) in people with less frequent social contact at baseline assessment compared to those with more frequent social contact. However, the relatively short duration of follow-up in most of the included studies creates potential for reverse causation bias. I will describe this in detail, as well as other limitations of previous research in this area, in section 2.3.2.

Analysis of social network size (e.g. having 0-3 vs >8 social contacts) indicated that simply having a larger social network, rather than frequent engagement with social contacts was not associated with dementia risk (pooled RR of dementia in people with smaller social network = 0.99 (0.95, 1.03), five studies). However, other associated domains were also associated with reduced risk of dementia; RR = 1.41 (1.13, 1.75) in those with less participation in social activities (six studies), RR = 1.58 (1.19, 2.09) for people reporting loneliness (three studies), and RR = 1.25 (0.96, 1.62) for those with low satisfaction with their social networks (four studies) (Kuiper et al., 2015).

In another systematic review of observational studies (Kuiper et al., 2016), higher risk of cognitive decline, the core symptom of dementia, was also associated with low level of engagement with structural aspects of social relationships. In this study, the

association between either social network size or social activity at baseline assessment and cognitive decline during the subsequent 1 to 15 years was examined. The pooled odds ratio from 19 studies of cognitive decline in people with lower engagement in structural social relationships was 1.08 (1.05, 1.11), with sensitivity analyses suggesting that small social network size (OR = 1.42 (1.11, 1.80) from three studies) was more important than low social activity (OR = 1.08 (1.04, 1.11) from 18 studies).

2.3.1 Potential mechanisms for protective effect of social contact

Having more frequent social contact could plausibly result in reduced risk of cognitive decline and dementia through one or more mechanisms. Social contact may reduce dementia risk by building cognitive reserve. Socialisation is often cognitively demanding, requiring deployment of numerous social cognitive domains (Turkstra, 2008), as well as planning, memory, and language, so it may exercise cognitive domains, thereby reducing vulnerability to decline in late life (Scarmeas and Stern, 2003). A post-mortem study of 89 older Americans found that higher levels of monthly social contact assessed, on average, 3 years before death modified the relationship between neuropathology and cognition, such that more amyloid load and neurofibrillary tangle density was less strongly associated with cognitive decline in people who had more frequent social contacts (Bennett et al., 2006b). This suggests that cognitive reserve had been enhanced in those with more frequent social contact.

However, considering the cognitive demands of socialisation, it may also be that having more social contact is a marker of higher baseline cognitive reserve, rather than causing greater reserve. Individuals with better childhood and early adult cognitive abilities may be able to develop greater social networks which are maintained into mid and late life, and it may be the greater early cognitive ability, rather than social contact, reduces subsequent dementia risk. This emphasises the need to take into account baseline cognitive status, such as through consideration of education, as a potential confounding variable.

Social contact could also affect dementia risk through the stress response; less social contact with others is associated with biological stress markers including disruption of cortisol responses (Stafford et al., 2013). A detrimental effect of stress on hippocampal networks has been demonstrated in animal models (Rothman and Mattson, 2010), and persistent midlife stress has been associated with elevated dementia risk in epidemiological studies (Johansson et al., 2013), suggesting that social isolation may affect dementia risk through the pathological effect of stress.

Social contact could also affect subsequent dementia risk by encouraging healthier lifestyle. Social isolation is associated with increased mortality through health behaviours such as smoking (Elovainio et al., 2017a) and cardiovascular illnesses (Holt-Lunstad et al., 2015). All-cause dementia and dementia subtypes are related to cardio- and cerebrovascular health (as described in section 2.1.1) (Larson et al., 2006, Barberger-Gateau et al., 2007), so the mechanisms by which low social contact is associated with cardiovascular risk factors and illness may also extend to dementia risk. Contact with others may model and encourage better health behaviours, leading to lower risk of vascular disease and subsequent better cognitive health and lower dementia risk.

2.3.2 Limitations of existing literature and potential for reverse causation bias

However, previous observational research examining the association between social network contact and cognitive decline and dementia is at risk of reverse causation or protopathic bias. Seven of eight previous studies examining the association of social contact and dementia risk had a mean follow-up of less than 4 years and none included a 'wash-out' period, whereby those who developed dementia within initial follow-up period were excluded from analysis in case reduced social contact was caused by the early symptoms of dementia (Kuiper et al., 2015). The one study which followed participants for 10 years (He et al., 2000), finding association between 'visiting friends' and lower dementia risk, did not provide methodological detail about the ascertainment or categorisation of their binary social variable. Fifteen of the 19 studies examining social contact and cognitive decline had average follow-up less than 5 years (Kuiper et al., 2016). Another recent study with 9 years of follow-up, not

included in the previous meta-analysis, found that greater social engagement was associated with lower dementia risk (Zhou et al., 2018). However, this study ascertained dementia status from self- or carer-report which is likely to underestimate dementia and be systematically biased.

Taken together, it is likely that most previous studies have overestimated the association by measuring social contact during a time of social decline resulting from the prodromal phase of dementia development. Neuropathological damage precedes dementia diagnosis by up to 20 years in neurodegenerative dementias (Jack et al., 2010), and early changes in ability to complete daily activities has been shown to emerge 5 to 6 years prior to dementia (Amieva et al., 2008), so it is conceivable that any association found during this period may indicate a consequence, rather than cause, of dementia.

Another study examining 2,513 Japanese-American men supported this hypothesis (Saczynski et al., 2006). In this cohort, a composite measure of social participation at 50 years of age was not associated with incident dementia 24 years later (hazard ratio (HR) = 1.08 (0.60, 1.92)), whereas a slightly modified assessment in the same population at age 70 was associated with dementia risk 4 years later (HR = 2.34 (1.18, 4.65)), supporting the importance of taking into account follow-up duration. The authors concluded social engagement had already been reduced by dementia. Furthermore, decrease in social contact from 50 to 70 was associated with dementia compared to those with consistently high social contact (HR = 1.87 (1.12, 3.13)), whereas consistently low social contact at 50 and 70 was not (1.65 (0.94, 2.90).

This study therefore suggests that reduction in social participation was an early feature of dementia as, if low social participation were a risk factor then consistently low participation would be expected to result in increased dementia risk, as these individuals would have had the longest duration of exposure to the risk factor. However, the point estimates of HR for decreasing and consistently low social contact are similar and with wide confidence intervals, suggesting that there may have been limited power to differentiate between risk in these groups. Also, this study used

composite measures of social participation, combining community activities and social contact, and the measures were different between mid- and late-life, making it difficult to determine which aspects of social participation were important. Furthermore, the authors did not adjust for the time between the late-life and dementia assessments, meaning that different follow-up duration for those with and without dementia could have affected results.

2.3.2.1 Potential mechanisms for social contact decline being an early consequence of dementia

Impairments in social function are characteristic of established dementia. 'Impairment in social or occupational functioning', accompanying cognitive decline is part of World Health Organisation dementia diagnostic criteria (World Health Organisation, 2004). Ratings by family carers of people with dementia indicate that increasing dementia severity is associated with spending less time with others (Budgett et al., 2019). Dementia causes impairments in emotion recognition (Halberstadt et al., 2011) and theory of mind (Bailey et al., 2008), through disruption of amygdala and frontal cortex networks (Chiong et al., 2013). Apathy is also a common and persistent symptoms of dementia (Van Der Linde et al., 2016).

Other symptoms which are likely to cause social functional decline, such as low mood, disinhibition and impulse control deficits, may be evident in the prodromal period, as described in the emergent concept of mild behavioural impairment (MBI) (Ismail et al., 2016). MBI describes a syndrome whereby behavioural symptoms, including socially inappropriate behaviours and decreased motivation accompany cognitive impairment. People with MBI are at high risk of dementia onset, as this is likely a prodromal syndrome for dementia (Taragano et al., 2009). Social changes have also been shown to occur in established dementia, with a Japanese observational study showing that people living in care homes decline in their ability to engage meaningfully in conversation with others and in organised care home social activities (Yokoi and Okamura, 2013). I have conducted qualitative interviews with people with dementia living in their own homes and their family carers who report social changes

occurring in mild dementia and around the time of diagnosis (Sommerlad et al., 2017).

2.3.2.2 Approaches to address limitations of previous studies

Studies with repeated measures of contact with social network over a long period which allow characterisation of social contact prior to dementia prodrome are needed to establish whether frequency of social contact is associated with dementia. Furthermore studies need to be adequately adjusted for premorbid health state and behaviours. In a meta-analysis of the association between social contact and mortality, analyses of the association between social contact and mortality which did not adjust for baseline health status, or exclude people who have pre-existing health conditions, had higher estimates of relative risk of death related to low social contact (OR = 1.53 (1.38, 1.70)) than adjusted studies (1.30 (1.16, 1.46) (Holt-Lunstad et al., 2015).

In addition, previous studies have combined different types of social contact, such as with friends, relatives and work colleagues, making it difficult to determine the active ingredient of any putative protective effect of social contact. The nature of social contact with these diverse networks is likely to differ, so one may confer benefit by for example, cognitive stimulation, stress reduction, or encouraging healthy lifestyle behaviours, while others may not. Therefore disentangling which aspects of social contact, if any, are beneficial is important. In addition, it is possible that contact with relatives increases in order to provide support in the prodromal phase of dementia; (Shanas, 1979) therefore not distinguishing the type of social contact may obscure associations with dementia.

2.4 Summary

In this chapter, I have outlined the epidemiology of dementia, lifestyle and health-related risk factors for dementia and the influence of changing rates of these on prevalence rates for dementia. I have defined social contact and described the differences between social contact and related social domains, as well as challenges

in the measurement of social contact in research settings. I have described the links between social contact and health in general, and cognitive health and dementia specifically, and have outlined the limitations of existing research literature on this topic, highlighting the areas which I intend to address in this thesis. In the next chapter, I will describe the aims and objectives of this thesis.

Chapter 3: **Overall aims and objectives of thesis**

The overall aim of this thesis is to examine whether social contact leads to reduced risk of dementia and cognitive decline. I completed a systematic review and meta-analysis examining the association between dementia and marital status, which I used as a surrogate marker of cumulative lifetime social contact, which is less susceptible to reverse causation bias than previous studies examining social contact, as marital status is unlikely to change as a result of prodromal dementia symptoms. I will then report results of my study aiming to assess the validity of ascertaining dementia diagnostic status from electronic health records, as used in the Whitehall II study. I will finally report the results of my cohort study examining the association between social contact and dementia and cognitive decline using the Whitehall II study with up to 28 years of follow-up, as low level of social contact 28 years prior to dementia development is unlikely to reflect dementia prodrome.

I hypothesise that being married, compared to lifelong single, widowed or divorced will be associated with reduced risk of dementia and that higher level of social contact with friends and relatives will be associated with lower risk of dementia and slower cognitive decline.

My specific objectives for each study are:

- Marital status and risk of dementia: systematic review and meta-analysis

1. synthesise evidence from published studies which reported the association of marital status (married/co-habiting, widowed, divorced/separated, lifelong single) and dementia incidence
2. examine the extent to which any association between marital status and dementia is modified by socio-demographic factors, study design and methodological quality of the study

- Validation of dementia case ascertainment from electronic health records

1. analyse the sensitivity and specificity of dementia diagnosis recording in general hospitals, using secondary mental healthcare data as gold-standard diagnostic status
2. examine time trends in sensitivity and specificity of general hospital dementia diagnosis between 2006 and 2016
3. explore the association of marital status with true positive and true negative recording.

- Association of social contact frequency with risk of dementia and cognitive decline

1. test the association between social contact with friends and relatives at 50, 60, and 70 years of age and incident dementia
2. examine association between change in social contact and incident dementia
3. examine the association between social contact and subsequent cognitive decline

Chapter 4: **Marital status and risk of dementia: systematic review and meta-analysis**

4.1 Introduction

I carried out this systematic review of the association between marital status and dementia to add to the evidence about the influence of social contact on risk of dementia. It was published in *Journal of Neurology, Neurosurgery and Psychiatry* (Sommerlad et al., 2018b) (Appendix 1) and, through press release and subsequent interviews, discussed in newspapers, radio, television, podcast, and other public engagement events (see Impact statement).

A recent systematic review had examined the association of social contact frequency and dementia (Kuiper et al., 2015) so I judged that this study need not be repeated. However, as described in section 2.3.2, this systematic review's findings that more frequent social engagement was associated with dementia risk was susceptible to reverse causation bias due to the short duration of follow-up (seven of eight included studies followed participants for less than 4 years on average), meaning that dementia prodrome may have affected social contact frequency at time of assessment. I regarded marital status as a surrogate marker of cumulative lifetime social engagement, which was less prone to reverse causation as it is unlikely that prodromal symptoms of dementia would result in a change in marital status by, for example, becoming divorced or widowed.

Marital status has potential to affect dementia risk by increasing daily social interaction which may improve cognitive reserve (Stern, 2012). I found no studies which directly compared levels of daily social contact between married and unmarried people. However, married people are more likely to cohabit with one or more people than unmarried people. In the 2011 UK census, 2.9% of married people, lived alone compared to 12.1% of single, 56.9% of divorced and 75.2% of widowed people (Office for National Statistics, 2014). I could not obtain data excluding under-

18s, so the surprisingly low figure for single people living alone is likely due to children being counted as 'single'.

Furthermore, marriage has been found to be associated with larger neighbourhood social networks (Campbell and Lee, 1992). This is often attributed in sociological literature to the institutional role of marriage in society (Slater, 1963) meaning that married people are more integrated in community social networks. Marriage may therefore be associated with reduced dementia risk through more frequent social contact although other potential mechanisms include reduced harmful lifestyle behaviours, as marital status is associated with healthier behaviours (Joung et al., 1995, Fuller, 2010). A meta-analysis of observational studies found lower mortality for married than unmarried people (Manzoli et al., 2007); health of unmarried Americans is worse than that of married people (Fuller, 2010); being married is related to improved cancer survival (Kravdal, 2001); and widowhood is associated with disability in older people (Goldman et al., 1995). In addition, bereavement or divorce in people who had been married, may promote dementia development through stress, which is associated with cerebral pathology seen in Alzheimer's disease, including dendritic remodelling, neurogenesis, and long-term potentiation (Rothman and Mattson, 2010) and associated with increased dementia risk (Johansson et al., 2013).

4.1.1 Aims and objectives

In this study, I therefore aimed to examine whether marital status affects risk of developing dementia. I hypothesised that married people are at lower risk of developing dementia compared to unmarried people and that previously married people are at lower risk than those who have been lifelong single.

My specific objectives were to:

1) Synthesise evidence from published studies which reported the association of marital status (married/co-habiting, widowed, divorced/separated, lifelong single) and dementia incidence

2) Examine the extent to which any association between marital status and dementia is modified by socio-demographic factors, study design and methodological quality of the study

4.2 Methods

I registered the study protocol prospectively in the PROSPERO register of systematic reviews:

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043161

4.2.1 Search strategy

I searched Embase, Medline and PsycInfo databases from their inception to 5th December 2016. My search terms (Appendix 2) identified papers whose titles, abstracts or keywords included terms encompassing marital status and dementia and I used the Scottish Intercollegiate Guidelines Network search term filters for observational studies (Scottish Intercollegiate Guidelines Network, 2017) to refine my search. I searched references of included studies and systematic reviews and contacted two experts in this field aiming to identify additional studies.

4.2.2 Study inclusion criteria

I included studies which:

1. used a prospective or retrospective cohort, case-control, or cross-sectional study design. I included studies using all these observational methodologies as this is acknowledged as best practice in meta-analysis (Stroup et al., 2000) and marital status, even if measured cross-sectionally, is likely to have been in place for many years previously.
2. reported quantitative data measuring the relationship between dementia and marital status or partner/spouse presence.
3. presented results of analyses which were adjusted for at least age and sex, because dementia is associated with female sex and older age and women

are likely to live longer and thus outlive their spouse. I contacted authors of studies which reported unadjusted results and included new adjusted data, if provided.

4. measured and reported marital status separately from other aspects of social network, e.g. contact with other family.
5. used a sample consisting of at least 50% of individuals aged 65 years or over at time of dementia ascertainment. If a younger population was sampled, I included a study if it presented stratified results for an over-65 population.
6. derived its sample from a general community-dwelling population. For cohort studies, participants had to be screened for dementia at baseline and prevalent dementia cases excluded.
7. were published research papers or dissertations. When I found relevant conference abstracts, I contacted the author for details of any eligible published research.
8. were published in English.

When two studies reported different analyses of cohort studies, to avoid duplication I used only the analysis which had a longer follow-up duration.

4.2.3 Data extraction

I screened the abstracts of all studies to identify those potentially meeting the inclusion criteria and reviewed full-text articles to confirm eligibility. A second researcher, Joshua Ruegger (JR) reviewed a random sample of 10% of the studies to assess agreement on exclusion and reviewed all included studies to approve eligibility. I used a standardised form (Appendix 3) to extract data for evidence synthesis. Extracted information included results and information for the assessment of the risk of bias.

In the one study (Seidler et al., 2003) which used lifelong single people as the reference group, I inverted the odds ratios. For this study and another (Beard et al., 1992), I calculated confidence intervals based on raw published data (Morris and Gardner, 1988). Where marital status categories had been combined (e.g. divorced

and single people) or results for dementia subtypes rather than all-cause dementia presented, I requested additional data from study authors. I have included new data for three papers (Bae et al., 2014, Bickel and Cooper, 1994, Fratiglioni et al., 2000).

4.2.4 Quality assessment

I rated methodological quality of included studies using an adapted version of the *Newcastle-Ottawa Criteria* (Wells et al., 2000) for cohort and case-control studies and the *Joanna Briggs Institute's Checklist* (Institute, 2016) for cross-sectional studies. Full details are in Appendix 4. In summary, these tools rated the quality of selection, measurement and comparability for all studies and gave a score for cohort and case-control studies (maximum of 9) and cross-sectional studies (maximum 6). Two researchers (JR and me) assessed the quality of all included studies and discussed discrepancies until consensus was reached.

4.2.5 Data analysis

I provide a narrative synthesis of findings from all included studies. Additionally, I combined results from studies which used the same measurements and similar methodology to calculate random-effects pooled relative risk estimates. I used the random-effects model of meta-analysis (DerSimonian and Laird, 1986) for two reasons. Firstly, it allows for measures of relative risk derived from different analytic methods, specifically in this analysis hazard ratios (HR) and odds ratios (OR), to be incorporated into the same meta-analysis (Fu et al., 2011). Additionally, I judged that there may be heterogeneity between studies, due to different underlying populations being included meaning that the true association may vary in different populations, and due to chance. The random-effects model accounts for such heterogeneity by applying a random-effects variance component derived from the extent of variability between effect sizes of the included studies.

All included studies provided an estimate of relative risk and confidence interval which I used for the analysis. I measured heterogeneity between the studies using the χ^2 test and the I^2 statistic and considered, a priori, that $I^2 > 50\%$ indicated substantial heterogeneity, as suggested in previous research (Sedgwick, 2015).

Where studies provided estimates of relative risk from different multivariate models, I included the result from the model with the largest number of covariates.

4.2.5.1 Main analysis: Widowed, divorced or single v married people and risk of all-cause dementia

My main analyses compared risk of all-cause dementia in married people to those who were widowed, divorced or lifelong single, for studies which ascertained dementia diagnosis status from clinical assessment, rather than from clinical registers. I chose to use studies with this ascertainment method as there is potential risk of bias using clinical registers (Herrett et al., 2010) as these rely upon patients accessing a clinical service and being accurately diagnosed, but marital status may affect this as unmarried people may not be encouraged to seek medical attention for symptoms of dementia, and may lack an informant to provide collateral information to the clinician.

4.2.5.2 Secondary analyses

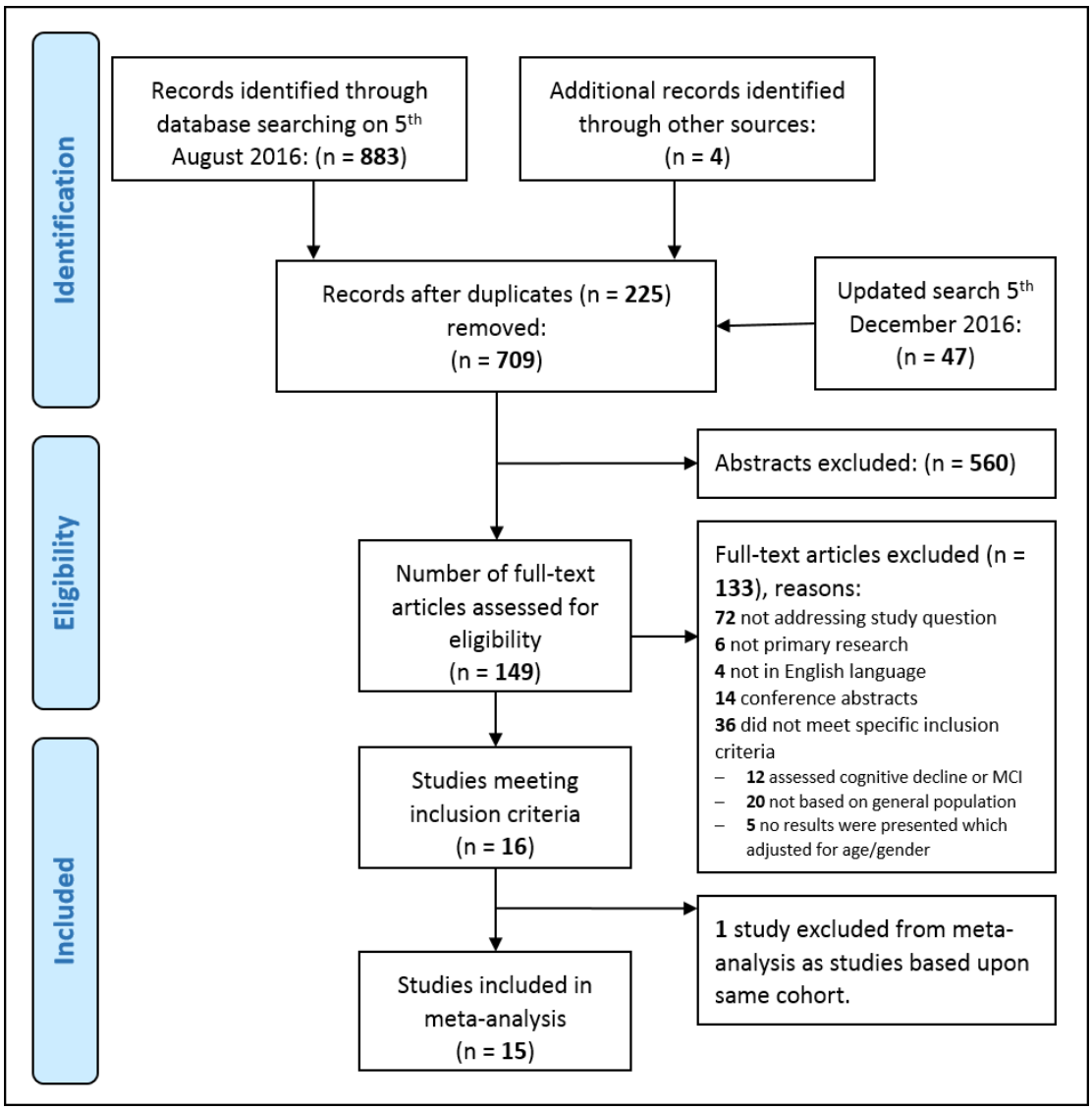
I conducted pre-specified secondary analyses. I analysed the association between marital status and risk of Alzheimer's or vascular dementia. I conducted stratified analyses and used meta-regression (Thompson and Higgins, 2002) to quantify the effect of four study design factors on the association between marital status and all-cause mortality: 1) dementia case ascertainment method – clinical assessment of study participants vs clinical register data; 2) study type – cohort v other studies; 3) study quality rating; 4) time-period of study conduct, based on mean year of birth of study participants.

I assessed the effect of confounder adjustment on the relative risk using stratified meta-analyses of studies which adjusted only for age and sex v studies which additionally adjusted for education or baseline cognition v studies which additionally adjusted for physical health. Few studies had also adjusted for level of social network contact, so I was unable to meta-analyse these but I provide a narrative synthesis of these findings. I assessed for evidence of publication bias using funnel plots and Egger's weighted regression method (Sterne et al., 2001).

4.3 Results

The PRISMA diagram (Figure 4-1) shows my search results and reasons for study exclusion. Sixteen studies fulfilled the inclusion criteria but I excluded one publication (Helmer et al., 1999) from my meta-analysis as it reported data from the same cohort as another study (Amieva et al., 2010a) but with shorter follow-up. The 15 studies in the analyses included 812,047 people, of whom 29,610 had any form of dementia. Of these, 61,012 had a clinical assessment for dementia and 751,035 had dementia status ascertained from clinical records.

Figure 4-1: PRISMA diagram of study identification and selection



Key study characteristics are described in Table 4-1. Nine were cohort studies (Amieva et al., 2010a, Arai et al., 2004, Bae et al., 2014, Bickel and Cooper, 1994, Fratiglioni et al., 2000, Hakanson et al., 2009, Hatch, 2013, Sundström et al., 2014, Sundström et al., 2016), two case-control (Beard et al., 1992, Seidler et al., 2003), and four cross-sectional (Correa Ribeiro et al., 2013, Fan et al., 2015, Guaita et al., 2015, Zhang et al., 2006). Eight included studies were set in European countries, four in Asia, two from USA and one from Brazil. The mean year of birth of study participants ranged from 1897 to 1939. Studies typically measured marital status at study inception (mean age 72.8 (standard deviation SD. 7.2 years.) In the cohort studies the duration of follow-up from marital status recording to dementia assessment was 3 to 20.9 (mean 8.5, s.d. 5.5) years.

Married people accounted for between 27.8% and 80.1% of the sample (widowed = 7.8 to 48.0%, divorced = 0 to 16%, lifelong single 0 to 32.6%). Two studies (Fan et al., 2015, Zhang et al., 2006) combined divorced and lifelong single people (6.1 and 10.1%). The mean methodological quality score for the cohort studies was 5.4/9; 2/9 for case-control studies; and 3.8/6 for cross-sectional studies. Full details of methodological assessment are in Appendix 4. All included cohort studies analysed complete cases, excluding participants who had withdrawn from study.

Marital status was, in all but two of the cohort studies which used registry data (Hatch, 2013, Sundström et al., 2016), reported by the participant or a close informant. No studies provided further details about this assessment, nor was there any information on duration of exposure to a particular marital status category. In one cohort study marital status was ascertained from a Swedish central population register (Sundström et al., 2016), and in another cohort a marriage registry was used to confirm marital status (Hatch, 2013). For the two case-control studies, those with dementia (or, if incapable of answering, an informant) were asked about their marital status at age 30 and 50 years and 10 years prior to interview (Seidler et al., 2003) or at time of diagnosis (Beard et al., 1992).

Table 4-1: Characteristics of included studies

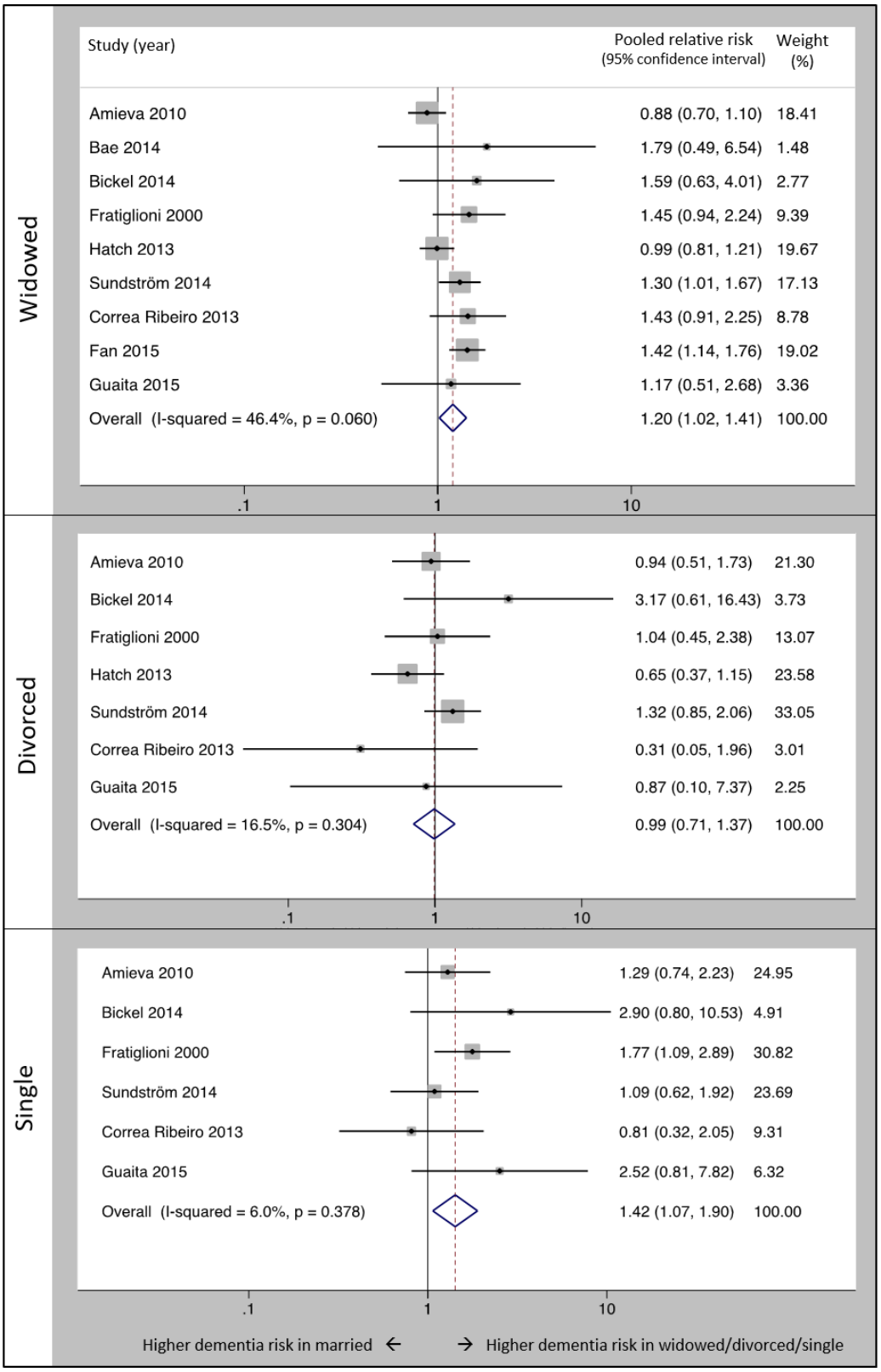
Study (First author and year of publication)	Study design	Country	Number of participants	Mean year of birth	Mean age at marital status evaluation (yrs)	Baseline marital status of participants (%)				Mean/ range of follow-up (yrs)	Method of dementia case-ascertainment	Quality rating
						Married	Widowed	Divorced	Single			
Amieva 2010	Cohort	France	2089	1914	74	60.7	32.5	2.7	4.2	5-15	Clinical assessment	5
Arai 2004	Cohort	Japan	853	1929	69	71	29 (unmarried)			5	Clinical assessment	3
Bae 2014	Cohort	S Korea	359	1936	72	70.2	29.8	0	0	3.5	Clinical assessment	3
Bickel 1994	Cohort	Germany	331	1918	74	42.4	47.5	3.8	6.4	7-8	Clinical assessment	5
Fratiglioni 2000	Cohort	Sweden	1368	1905	82	27.8	45.4	5.9	20.9	3	Clinical assessment	6
Håkansson 2009	Cohort	Sweden	2000	1926	51	80.1	7.8	4.4	7.8	20.9	Clinical assessment	8
Hatch 2013	Cohort	USA	5092	1920	75	65.9	29.9	4.1	N/A	12	Clinical assessment	8
Sundström 2014	Cohort	Sweden	1677	1919	75	57.6	14.2	5.7	32.6	8.6	Clinical assessment	7
Sundström 2016	Cohort	Sweden	750129	1928	69	64.9	8.4	16.0	10.8	6	Clinical register / death register	9
Beard 1992	Case-control	USA	482	1897	80	28.8	48.0	5.4	17.8	N/A	Secondary care clinical register	3
Seidler 2003	Case-control	Germany	424	1924	77	78.5	11.1	3.8	6.6	N/A	General practice clinical register	2
Correa-Ribeiro 2013	Cross-sectional	Brazil	683	1931	78	41.6	40.8	7.5	10.1	N/A	Clinical assessment	3
Fan 2015	Cross-sectional	Taiwan	10432	1936	76	64.2	31.0	4.8 (Div / single)		N/A	Clinical assessment	4
Guaita 2015	Cross-sectional	Italy	1321	1939	72	67.1	24.6	2.2	6.1	N/A	Clinical assessment	4
Zhang 2006	Cross-sectional	China	34807	1929	68	77.4	20.8	1.6 (Div / single)		N/A	Clinical assessment	4

All but three of the studies clinically examined all participants to ascertain diagnostic status (outcome). The other studies (Sundström et al., 2016, Seidler et al., 2003, Beard et al., 1992) ascertained diagnostic status from routine clinical registers and, for one of these studies (Sundström et al., 2016), death registers. Except for the cohort study (Sundström et al., 2016) which exclusively used register data, none reported whether they ascertained dementia status from death registers. The clinical examination used in the majority of studies was a staged approach: a screening phase followed by a more detailed neuropsychological and functional assessment and an expert consensus panel to establish diagnostic status.

4.3.1 Main meta-analysis: Widowed, divorced or single v married people and risk of all-cause dementia

For the primary meta-analysis, I pooled risk estimates from studies which evaluated the risk of all-cause dementia according to marital status category, with dementia case ascertainment based upon clinical examination (all meta-analyses are shown in Figure 4-2). Nine studies which included 23,352 people analysed the risk of all-cause dementia in widowed v married people and I found that in widowed, compared to married, people, the relative risk of dementia = 1.20 (95% CI 1.02, 1.41). The relative risk for divorced v married people from 7 studies including 12,561 people = 0.99 (0.71, 1.37); for the 6 studies including 7,469 people which analysed dementia risk for lifelong single people, RR = 1.42 (1.07, 1.90).

Figure 4-2: Forest plot showing pooled relative risk of dementia in widowed, divorced and single people v married people when dementia ascertained by clinical examination



Notes: Figures are based on random-effects meta-analysis; Included studies ascertained dementia diagnostic status using a clinical examination of study participants.

4.3.2 Secondary analyses

4.3.2.1 Widowed, divorced or single v married people and risk of Alzheimer's disease and vascular dementia

Fewer studies examined the risk of dementia subtypes according to marital status. Eight examined the risk of Alzheimer's disease (1,891 cases) in widowed v married people and found a similar magnitude but non-significant pooled relative risk of 1.24 (0.97, 1.60).(Amieva et al., 2010a, Bae et al., 2014, Hakanson et al., 2009, Hatch, 2013, Beard et al., 1992, Seidler et al., 2003, Guaita et al., 2015, Zhang et al., 2006) The risk of Alzheimer's disease in five (Amieva et al., 2010a, Hatch, 2013, Beard et al., 1992, Seidler et al., 2003, Guaita et al., 2015) studies of divorced (0.89 (0.58, 1.36)) and three (Amieva et al., 2010a, Beard et al., 1992, Guaita et al., 2015) of lifelong single (1.07 (0.75, 1.52)) people was not different to that of married people.

For vascular dementia (372 cases), no effect of marital status on dementia risk was found in pooled estimates from the three studies (Seidler et al., 2003, Guaita et al., 2015, Zhang et al., 2006) which examined the risk for widowed v married people (pooled RR = 0.90 (0.40, 2.04)) or the two (Seidler et al., 2003, Guaita et al., 2015) which examined risk in lifelong single people v married (2.66 (0.85, 8.28)). Only one study (Seidler et al., 2003) compared the risk of vascular dementia in divorced and married people and found no difference.

4.3.2.2 Widowed, divorced or single v married people and risk of all-cause dementia, stratified by sex

Two studies analysed the relationship between marital status and dementia separately for men and women. For one (Sundström et al., 2016) the outcome was all-cause dementia and for the other (Beard et al., 1992), it was Alzheimer's disease so meta-analysis was not possible. Neither study found any difference between men and women in the association of marital status and dementia. The first of these studies was based on clinical and population register data and found a similar risk of dementia for single, widowed, and divorced, men and women. The second study, which was a case-control study using Alzheimer's disease as the outcome of interest,

had small numbers of participants and the resultant wide confidence intervals overlapped for men and women, also indicating no significant differences in risk by sex.

4.3.2.3 Impact of study design on association between marital status and all-cause dementia

I examined whether different aspects of study design affected the associations found in my meta-analyses.

4.3.2.3.1 Widowed, divorced or single v married people and risk of all-cause dementia, stratified by method of dementia case ascertainment

There was evidence that the method of dementia case ascertainment affected the risk estimates (Table 4-2). Studies using clinical examination for dementia ascertainment produced higher pooled estimates for the effect of being widowed (1.20 (1.02, 1.41) v 1.12 (1.07, 1.18)) or lifelong single (1.42 (1.07, 1.90) v 1.23 (1.17, 1.29)) and this difference nearly reached significance for the comparison of single and married people (p=0.06). The risk of dementia for divorced compared to married people was slightly lower but the risk estimates for studies using either methods of were ascertainment were not significant.

4.3.2.3.2 Widowed, divorced or single v married people and risk of all-cause dementia, stratified by study type

The pooled risk estimate (Table 4-2) for dementia in widowed v married people was lower (meta-regression p=0.004) from the seven cohort studies (1.10 (1.05, 1.28)) (Amieva et al., 2010a, Bae et al., 2014, Bickel and Cooper, 1994, Fratiglioni et al., 2000, Hatch, 2013, Sundström et al., 2016, Sundström et al., 2014) than the four cross-sectional or case-control studies (1.39 (1.16, 1.67)) (Seidler et al., 2003, Correa Ribeiro et al., 2013, Fan et al., 2015, Zhang et al., 2006) which examined this association. There were no differences between cohort and other studies in pooled estimates of dementia risk in lifelong single v married people or divorced v married people.

Table 4-2 Meta-regression of the risk of all cause dementia according to marital status, stratified by study time-period, case ascertainment methodology, study type and study quality.

		Widowed v Married		Divorced v Married		Single v Married	
		Stratified analysis: Relative risk (95% CI) Number of studies	Meta-regression coefficient (95% CI) p-value	Stratified analysis: Relative risk (95% CI) Number of studies	Meta-regression coefficient (95% CI) p-value	Stratified analysis: Relative risk (95% CI) Number of studies	Meta-regression coefficient (95% CI) p-value
Method of case ascertainment	**Clinical assessment**	1.20 (1.02, 1.41) n = 9	b = -0.06 (-0.18, 0.05) p=0.29	0.99 (0.71, 1.37) n = 7	b = 0.34 (0.06, 0.62) p = 0.02	1.42 (1.07, 1.90) n = 6	b = -0.27 (-0.55, 0.01) p = 0.06
	Clinical registers	1.12 (1.07, 1.18) n = 2		1.11 (0.52, 2.38) n = 2		1.23 (1.17, 1.29) n = 2	
Study type	**Cohort**	1.10 (1.05, 1.28) n = 7	b = 0.28 (0.09, 0.46) p = 0.004	1.16 (0.87, 1.55) n = 6	b = -0.83 (-1.69, 0.03) p = 0.06	1.24 (1.17, 1.30) n = 5	b = 0.08 (-0.45, 0.62) p = 0.76
	Case-control / cross-sectional	1.39 (1.16, 1.67) n = 4		0.55 (0.23, 1.31) n = 3		1.21 (0.67, 2.18) n = 3	
Global quality score	**Higher quality ≥6**	1.13 (1.02, 1.31) n = 4	b = 0.08 (-0.06, 0.23) p = 0.27	1.16 (0.83, 1.62) n = 4	b = -0.40 (-0.88, 0.08) p = 0.10	1.26 (1.09, 1.45) n = 3	b = 0.20 (-0.17, 0.57) p = 0.29
	Lower quality <6	1.22 (0.96, 1.54) n = 7		0.88 (0.54, 1.44) n = 5		1.33 (0.92, 1.92) n = 5	
	Increase in quality by one point	b = -0.04 (-0.08, -0.002) p = 0.04 n = 11		b = 0.12 (0.01, 0.24) p = 0.04 n = 9		b = -0.05 (-0.13, 0.03) p = 0.21 n = 8	
Time period	**Mean year of birth before 1927**	1.11 (0.93, 1.31) n = 6	b = 0.15 (-0.14, 0.43) p = 0.32	0.98 (0.71, 1.37) n = 6	b = 0.35 (0.08, 0.63) p = 0.01	1.40 (1.06, 1.85) n = 5	b = -0.22 (-0.50, 0.06) p = 0.13
	Mean year of birth after 1927	1.23 (1.06, 1.43) n = 5		1.08 (0.50, 2.35) n = 3		1.24 (0.94, 1.62) n = 3	
	Mean year of birth ten years later	b = 0.08 (-0.08, 0.23) p = 0.34 n = 11		b = 0.24 (0.01, 0.47) p = 0.04 n = 9		b = -0.15 (-0.33, 0.02) p = 0.09 n = 8	

Notes: Figures are based on random-effects meta-analysis

4.3.2.3.3 Widowed, divorced or single v married people and risk of all-cause dementia, stratified by study quality

Stratified analyses of higher v lower quality studies and meta-regression analysis of the effect of study quality on risk estimates found no effect of study quality on relative risk for widowed or lifelong single people. The four higher quality studies (Fratiglioni et al., 2000, Hatch, 2013, Sundström et al., 2016, Sundström et al., 2014) produced a slightly increased risk for divorced people than the five lower quality studies (Amieva et al., 2010a, Bickel and Cooper, 1994, Seidler et al., 2003, Correa Ribeiro et al., 2013, Guaita et al., 2015) but in neither stratum was divorce related to dementia risk.

4.3.2.3.4 Widowed, divorced or single v married people and risk of all-cause dementia, by time-period

Meta-regression analysis suggested that the relative risk of dementia in divorced people increased by 24% (95% CI 1, 47%) for studies of participants born ten years later (Table 4-2), although the risk remained non-significant when comparing the newer and older studies. There was some evidence that time-period modified the effect of being lifelong single on risk of dementia: the risk of dementia in single people was 15% lower (95% CI 33% lower to 2% higher) for every ten years later that participants were born. In the oldest studies (participants born on average before 1927) the risk of dementia in lifelong single v married people was 1.40 (1.06, 1.85) and for the most recent studies (of people born after 1927), the risk was 1.24 (0.94, 1.62). No significant modifying effect of time-period was found for the risk of dementia in widowed people.

4.3.2.4 Effect of covariate adjustment on risk estimates.

For dementia risk in widowed v married people, the pooled risk estimates from the three studies (Bae et al., 2014, Bickel and Cooper, 1994, Sundström et al., 2014) which adjusted only for age and sex (1.33 (1.05, 1.69)) were higher than the five studies (Fratiglioni et al., 2000, Seidler et al., 2003, Correa Ribeiro et al., 2013, Guaita et al.,

2015, Hatch, 2013) which adjusted additionally for education or baseline cognitive function (1.12 (0.95, 1.31)) (Table 4-3). No further attenuation of the effect was found in three studies (Amieva et al., 2010a, Fan et al., 2015, Sundström et al., 2016) which additionally adjusted for physical health (1.12 (0.92, 1.37)).

For lifelong single people, the relative risk of dementia in single v married people fell from 1.45 (0.97, 2.19) to 1.23 (1.17, 1.29) in studies which adjusted for physical health but the risk estimate for dementia was not affected by adjustment for education.

Two studies adjusted analyses for level of social engagement, neither of which found significant association between being unmarried and incident dementia. One French cohort study included a range of social relationship measures, including size of social network and satisfaction with social network, as covariates and only presented the fully adjusted results which were non-significant (Amieva et al., 2010b). The other, a study of Taiwanese older people, presented results adjusted for social engagement, including participation in social activities, finding relative risk of dementia for single or divorced people compared to married to be 1.20 (0.73, 1.96) (Fan et al., 2015).

4.3.2.5 Publication bias

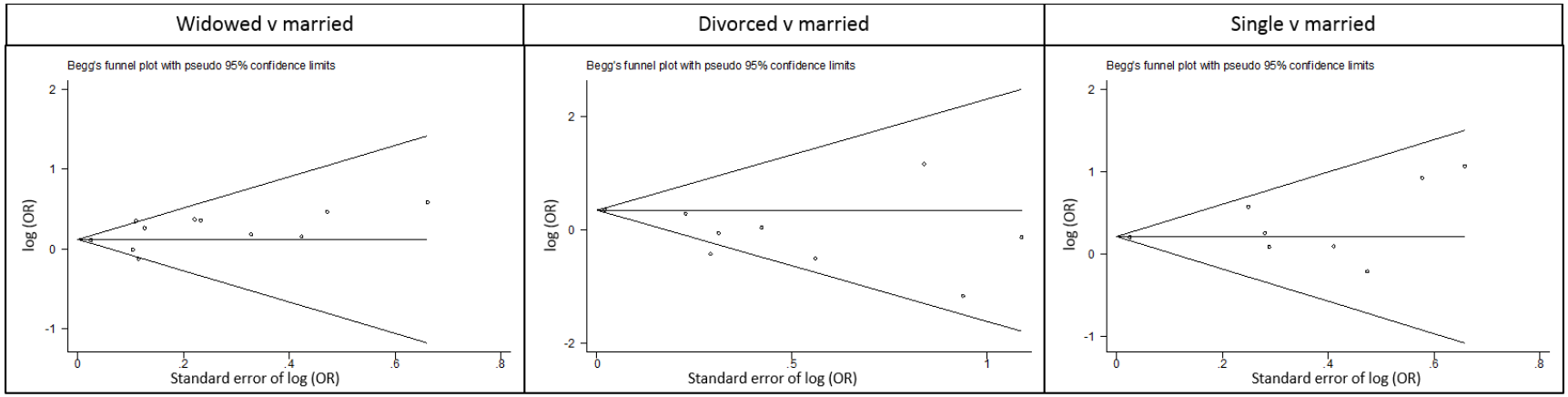
In funnel plots (Figure 4-3) there was no clear evidence of asymmetry suggesting publication bias. Weighted regression (Egger) test indicated that there was unlikely to be publication bias in studies examining widowed (p=0.30) or lifelong single (p=0.35) people but that there may have been for studies of divorced people (p=0.04).

Table 4-3 Meta-analyses of the risk of all cause dementia according to marital status, stratified by covariate adjustment.

	Widowed v Married		Divorced v Married		Single v Married	
	Relative risk (95% CI) p-value	**Number of studies Heterogeneity**	**Relative risk (95% CI) p-value**	**Number of studies Heterogeneity**	**Relative risk (95% CI) p-value**	**Number of studies Heterogeneity**
Studies adjusted for age and sex	1.33 (1.05, 1.69) p = 0.02	n=3 I^2 =0%	1.41 (0.90, 2.21) p = 0.14	n=2 I^2 =1.5%	1.49 (0.61, 3.63) p = 0.38	n=2 I^2 =46.1%
Studies adjusted for age, sex and education	1.12 (0.95, 1.31) p = 0.19	n=5 I^2=0%	0.70 (0.47, 1.06) p = 0.10	n=5 I^2=0%	1.45 (0.97, 2.19) p = 0.005	n=4 I^2=14.6%
Studies adjusted for age, sex, education, and physical health	1.12 (0.92, 1.37) p = 0.26	n=3 I^2=77.8%	1.30 (0.93, 1.81) p = 0.12	n=2 I^2=42.5%	1.23 (1.17, 1.29) p = 0.36	n=2 I^2=0%

Notes: Figures are based on random-effects meta-analysis

Figure 4-3 Begg's funnel plots for main meta-analyses showing risk for publication bias in published studies.



4.4 Discussion

This study summarised all accessible published evidence and added to these by contacting authors for new data. I found that people who are lifelong single have a 42% higher risk and that those who are widowed have a 20% higher risk of developing dementia than those who are married, in studies adjusted for age and sex. I found no evidence that dementia risk in divorced people differs from married people. The reduced risk in married people persisted in sensitivity analyses, indicating the robustness of the findings. Similar direction and magnitude of effect were found for dementia subtypes, but confidence intervals for these estimates were wider as these analyses had fewer participants.

Study design affects estimates of dementia risk. Higher relative risk of dementia for lifelong single and widowed people was found in studies which diagnosed dementia following clinical examination of all participants than in those which ascertained diagnostic status from routinely collected data; and lower risk was found for widowed people in cohort studies than in case-control or cross-sectional studies. There is some indication that the elevated risk in lifelong single people has decreased over time, with more recent studies finding smaller associations. I found that much, but not all, of the increased risk in widowed people is attenuated after adjustment for education and that confounding by physical health explains part of the increased risk of dementia in lifelong single people.

The association between marriage and reduced dementia risk meets several Bradford Hill criteria for causation (Hill, 1965); marriage precedes dementia development (temporality), results are similar in different studies and socio-cultural contexts (consistency), longer duration of being unmarried is associated with higher dementia risk, i.e. lifelong single vs widowed (biological gradient). However, it is not biologically plausible that the process of marriage itself has a direct causative relationship with dementia development, and the association lacks specificity as there are other potential explanations.

4.4.1 Potential explanations for findings

My findings may instead be explained in one or more of the following ways. First, being married may change individuals' exposure to other protective and risk factors throughout their subsequent lifespan – this is supported by my identification of factors which partially explain this risk, and evidence showing married people to be more likely to have a healthy lifestyle (Joung et al., 1995, Fuller, 2010). The residual increased risk for lifelong single people in studies which adjusted for age, sex, education and physical health may be due to higher levels of daily social contact with the spouse in married than single people. There are also possibly higher levels of contact with a wider social network (Campbell and Lee, 1992), and these social relationships may contribute to building cognitive reserve and reducing dementia risk over the lifespan.

Only two studies adjusted for level of social engagement and both found no association between marital status and dementia; this is consistent with this explanation, as it may suggest that once differential level of social contact is taken into account, dementia risk is similar between married and unmarried people. Additionally, the magnitude of effect of marital status on dementia is higher than the risk for mortality in unmarried compared to married people (RR=1.1) (Manzoli et al., 2007), supporting the idea that marriage's effect on dementia risk is more than just improving physical health and that there may a direct cognitive benefit of behaviours related to being married.

Second, the end of marriage through bereavement could act directly to increase dementia risk, through the detrimental effect of stress on hippocampal neurons (Rothman and Mattson, 2010) or cognition (Johansson et al., 2013) and this theory could explain the increased dementia risk for widowed, but not divorced, people, as studies have found widowhood to be more stressful than divorce (Gardner and Oswald, 2006, Holmes and Rahe, 1967). Third, the association between marital status and dementia could be confounded by other underlying cognitive or personality traits. In societies where marriage was the social norm, people with difficulties in flexibility of thought or communication and consequent smaller lifelong cognitive

reserve (therefore more likely to develop dementia) may be less likely to marry. This explanation is supported by the finding that the risk for lifelong single people is possibly reduced in more recent times. Remaining unmarried has become more common (Pew Research Centre, 2010, McLaren, 2016) and it may be that single people born in the latter half of the 20th Century do not have unusual cognitive and personality characteristics.

4.4.2 Strengths and limitations

These findings, from large populations across numerous countries and time-periods, are the strongest evidence yet that married people are less likely to develop dementia, and the nature of marital status being usually fixed over many years reduces chance of reverse causation bias affecting results. I searched the literature systematically, sought additional studies where possible by contacting authors to gain further data where published information was insufficient and followed PRISMA guidance in the conduct and reporting of this study (Stroup et al., 2000). The main limitations of this review relate to the methodology of included studies. I could not investigate the effect of the duration of being widowed or divorced as the included studies did not report this. In addition, I could only investigate the impact of potential confounders which were measured and analysed in studies, limiting my investigation of potential explanations for the findings. In particular, only two studies adjusted for level of social network contact frequency, meaning that it was not possible to examine in detail the potential mediating or confounding role of social contact in the association between marital status and dementia risk.

My findings in relation to divorced people are less robust as there were fewer divorced people in the included studies. While my search terms were thorough, supporting my belief that I identified all studies examining this relationship, I may have missed eligible studies. This is a particular risk for observational studies examining the effect of other exposures on dementia risk, which may have reported marital status as a potential covariate, although less likely for this review as I aimed to only include studies which adjusted the relationship between marital status and dementia for age and sex.

4.4.3 Conclusions

My finding of a 42% increased risk in lifelong single people compares closely to other known dementia risk factors incorporated in National Institute for Health and Care Excellence guidelines (NICE) (National Institute for Health and Care Excellence, 2015) such as physical inactivity (RR = 1.4) and less education, hypertension or smoking (RR for each = 1.6) (Norton et al., 2014). My findings support the need for further work to develop preventative approaches in these lifestyle domains and indicate this may be particularly important for widowed and lifelong single people who are higher-risk groups.

4.4.4 Implications of findings for research into social networks and use of electronic health records

I found indications that routine clinical registers may underestimate the risk of dementia in unmarried people, compared to those who are married, which is likely to be because of limited sensitivity of register data compared to research diagnoses (Jin et al., 2004) and unmarried people are more likely to be undiagnosed in routine practice (Savva and Arthur, 2015). Diagnosing dementia in people who attend clinic alone is more difficult, due to lack of collateral information and because individuals with dementia may not complain of memory impairment, (Livingston et al., 2010). I therefore completed further research, detailed in the next chapter, into the validity of using electronic health records to examine the association between social networks and dementia.

This study strengthened the hypothesis that social network contact confers protection against dementia. It also indicated to me that in my future research examining social network contact's influence on dementia risk, I would need to consider the role of marital status as a potentially important indicator of social engagement and other healthy lifestyle behaviours. Future research examining the link between marital status and dementia should 1) aim to evaluate the contribution of social contact and health behaviours; 2) use studies with sufficient follow-up to allow exploration of pre-marriage personality characteristics; and 3) use cohort

studies with sufficient detail on the duration of marriage, widowhood or divorce to allow the exploration of a dose-response effect.

Chapter 5: Validation of dementia case ascertainment from electronic health records

5.1 Introduction

Electronic health record databases containing demographic and clinical data collected during routine clinical practice are a potentially useful resource for epidemiological studies as they provide relatively cheap and accessible information on clinically relevant populations (Garratt et al., 2010). I plan to use the Whitehall II study (Marmot and Brunner, 2005) for my analysis of the effect of social contact on the development of dementia as this cohort's follow-up period is much longer than previous studies detailed in section 2.3.2 and I will explain my choice of this cohort further in section 6.1. However, Whitehall II uses routinely-collected electronic records to ascertain cases of dementia, rather than through standardised clinical examination of subjects. Three linked databases are used: Hospital Episode Statistics (HES), which are records from English general hospital inpatient and outpatient care; Mental Health Services Data Set (MHSDS), which are records from community-based mental healthcare; and Mortality Data, which includes diagnoses entered on death certificates. There have been concerns about the use of such databases as 1) information is not collected from whole populations, only on patients who have had clinical contact with the service which may vary systematically; 2) patients were assessed in routine clinical setting where practice may vary, therefore lacking the systematic rigour expected in research studies, such that diagnoses may be missed; 3) data may be missing or inaccurate (Mbizvo et al., 2018). I also found in my systematic review (section 4.3.2.3.1) that routine registers may underestimate the risk of dementia in unmarried people.

Five previous studies have examined electronic record sensitivity for dementia diagnosis compared to research cohort-derived gold-standard diagnostic assessment. Sensitivity estimates of hospital data from these studies have been between 26% and 43% in Swedish studies (Dahl et al., 2007, Feldman et al., 2012, Jin

et al., 2004), 51% in Finland (Solomon et al., 2014), and 70% in the US (Knopman et al., 2011). The wide variation in these estimates suggests that accuracy is likely to differ between databases, possibly related to different healthcare systems and changing patterns of diagnostic recognition and recording, indicating that validation of specific data is required to know the effect of their use; no previous study has examined HES data. In addition, previous studies have been relatively small, including between 23 and 498 people, and none have examined data later than 2008, nor examined trends over time. Recent health policy to increase timely diagnosis (Department of Health, 2009) and greater healthcare professional awareness of the condition may have increased accuracy of subsequent diagnostic recording in the UK.

I therefore conducted an observational study aiming to assess the validity of NHS dementia diagnostic data. I examined the accuracy of HES general hospital inpatient dementia records to explore whether there is systematic bias in the recognition of dementia in routine clinical care, as I judged that such systematic bias may be applicable to the three datasets used in Whitehall II. I compared HES records to a gold-standard secondary mental healthcare record, by calculating HES sensitivity and specificity, whether recording accuracy has changed over time, and whether accurate dementia recording is associated with marital status, which I used as a surrogate marker of social contact.

The study detailed in this chapter was published in *Alzheimer's and Dementia* in April 2018 (Sommerlad et al., 2018a) (Appendix 5).

5.1.1 Aims and objectives

I sought to investigate the accuracy of recorded diagnoses of dementia in general hospitals in the UK, using data up to 2016. In particular, I aimed to:

1. analyse the sensitivity and specificity of dementia diagnosis recording in general hospitals, using secondary mental healthcare data as gold-standard diagnostic status

2. examine time trends in sensitivity and specificity of general hospital dementia diagnosis between 2006 and 2016
3. explore the association of marital status with true positive and true negative recording.

5.2 Methods

5.2.1 Study setting and data source

I conducted an observational cohort study using data from two linked datasets of routinely-collected clinical data, described below.

5.2.1.1 The South London and Maudsley National Health Service (NHS) Foundation Trust Biomedical Research Centre Case Register 'Clinical Record Interactive Search' (CRIS) data extraction tool.

The CRIS data resource provides pseudonymised electronic medical records from all patients seen in South London and Maudsley NHS Foundation Trust. This NHS trust is one of Europe's largest secondary mental healthcare providers which delivers a range of psychiatric care, including dementia assessment and management in memory clinics, to a catchment area containing 1.2 million residents in four south London boroughs.

I used the CRIS data as the resource from which to derive 'gold-standard' dementia cases. I could find no published data reporting specifically the proportion of people with diagnosed dementia who have been seen in these secondary mental healthcare records. However, nationwide, memory clinics such as those included in the CRIS data are the primary dementia diagnostic service in the UK (Department of Health, 2009), whose practice is to take referrals from other health and social care services (usually primary care) of people who have been identified as having possible dementia. National dementia recording rates are estimated to be around 68%. This figure is the proportion of people with a dementia diagnosis nationally, compared to the number predicted to have dementia, using the Cognitive Function and Aging II study, which is a large UK prevalence study (Matthews et al., 2013). Estimates for my study's

catchment area based on the local age demographics, are similar (between 68 and 77% in the four boroughs comprising the catchment area (NHS Digital, 2018). This suggests that the CRIS record is likely to encompass and closely resemble most of those with diagnosed dementia in the large inner-city and suburban catchment area.

In CRIS, pseudonymised data are extracted from structured fields in patients' electronic clinical records. Data are also obtained from unstructured text within clinical records, such as correspondence and case notes, using a natural language processing algorithm based on General Architecture for Text Engineering (GATE) software (Cunningham, 2002), which generates text strings associated with diagnostic statements. This means that a diagnosis being recorded in CRIS does not rely upon a clinician entering that diagnosis within the structured field of an electronic health record. If the clinician documents the diagnosis within the general text of a clinic letter or clinical progress note, as is common, then the GATE algorithm is able to extract the diagnosis, with ability to discriminate between positive and negative diagnostic statements (Perera et al., 2016a).

The GATE algorithm for diagnosis of vascular dementia has previously been found to have 99% precision (equivalent to positive predictive value, the proportion of derived diagnoses which are judged to have correctly identified dementia) and 98% recall (equivalent to sensitivity, the proportion of dementia cases correctly identified by the algorithm) (Perera et al., 2016a). The GATE algorithm has been used to examine a variety of dementia-related research questions using this dataset (Perera et al., 2016a, Ward et al., 2015) and also applied in other secondary mental health care data (Aworinde et al., 2018). Data are available for all clinical records from 1st January 2006 and CRIS is linked to the Hospital Episode Statistics (HES) database, described below.

5.2.1.2 National Health Service (NHS) Digital Hospital Episode Statistics (HES)

This dataset contains clinical information about NHS care, collected directly by hospital providers and has been used in numerous previous studies (Aylin et al., 2013, Gunnell et al., 2012, Kapur et al., 2013). The data of interest for this study are records of general (non-psychiatric) inpatient admissions to any hospital in England and the

clinical diagnoses recorded on each hospital discharge summary by the treating clinical team. Diagnoses are recorded as International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (World Health Organisation, 2004) codes and each admission has up to 20 diagnostic codes. The method of admission (emergency or elective) is also recorded (Health and Social Care Information Centre, 2017).

Diagnoses recorded in HES are those clinically identified during the admission, obtained from correspondence with primary care, or derived from pre-existing clinical records such as previous hospital medical records – some record systems pre-populate diagnosis fields with previously recorded chronic conditions. There was no routine practice of dementia assessment in English hospitals until 2012. Then the UK Department of Health recommended case-finding in inpatients aged 75 years or older for possible dementia, by asking if any admitted person had experienced change in their memory lasting a year to the extent that it influenced functioning. This would be followed, if dementia was suspected, by referral to memory services, (Department of Health, 2012) although I was not able to find data reporting the extent of adoption of this practice.

5.2.2 Study participants

I obtained records from CRIS of all patients aged 65 years or over who had been assessed (as part of ongoing follow-up or as first clinical contact) during the study window from 1st January 2008 to 31st March 2016. I did not include patients whose first electronic record of dementia was during 2006-7 as I aimed to identify people with newly diagnosed dementia rather than those with a history of the condition. Those whose first CRIS recording was before 2008 would include many whose dementia was diagnosed before the inception of the dataset, but whose diagnoses were retrospectively recorded when electronic records started and they were being followed up during 2006-7.

These data were linked to HES records over the same period. All mental health and dementia diagnoses in CRIS were extracted from structured fields in the electronic

medical record where clinicians are required to record ICD-10 (World Health Organisation, 2004) codes, or from unstructured text using the GATE software, including dementia diagnosis (coded in CRIS as F00x-F03x). I retrieved the dates of, and diagnoses recorded for, each general hospital admission during the study window, including diagnosis of dementia (coded in HES as F00x-F03x, G30x, G31.0 or G31.8).

5.2.3 Covariates

I retrieved data from CRIS on participants' age, sex, ethnicity (White, Asian, Black African/Caribbean, other); marital status (married, widowed, divorced, single); and last recorded dementia sub-type (Alzheimer's disease, vascular dementia, Lewy body dementias, other dementia (encompassing any other specified dementia type), unspecified dementia (where dementia aetiology was not recorded)). I estimated socioeconomic status using the 2010 Index of Multiple Deprivation (IMD), which is a measure based on 37 indicators related to the patient's most recent address (Department for Communities and Local Government, 2015), with a higher score indicating more socioeconomic deprivation.

Cognitive severity was estimated from the most recently recorded Mini Mental State Examination (MMSE) (Folstein et al., 1975) score at the time of hospital admission. Other aspects of clinical presentation were derived from CRIS using the Health of the Nation Outcome Scale (HoNOS) which is a standard instrument applied routinely in mental health care with adequate to good psychometric properties (Pirkis et al., 2005). It comprises 12 subscales rating problems with agitation; self-injury; alcohol/drug use; cognition; physical illness; hallucinations; depressed mood; relationships; daily living function; living conditions; occupation or activities; other problems. Each domain is rated 0 (no problem) to 4 (severe or very severe problem). As ≥2 is seen to indicate a clinically significant problem, I dichotomised the HoNOS scores in each domain to facilitate interpretation: scores of 0 and 1 were grouped as no/minor problems, scores of ≥2 indicated significant problem in that domain. I did not use the HoNOS cognitive subscale in my primary analyses due to its correlation with MMSE, or the 'other' subscale due to its non-specific clinical meaning.

All covariates were derived from the time closest to the index hospital admission.

5.2.4 Data extraction and cleaning procedure

To acquire the data, I completed a data specification request form, specifying the variables required from the CRIS and HES databases. I met with a data scientist to refine the request and they extracted the data from the CRIS server. As the data were routinely recorded, not specifically for research use, they required cleaning to harmonise variable definition and process variables for use in statistical software. I also examined the accuracy of important variables, including date of death in relation to diagnosis and hospital admission, and CRIS diagnostic coding. Ninety-five participants who had CRIS diagnosis recorded over six months after the recorded date of death were excluded, as I considered that the date of death or diagnostic status would be unreliable as diagnosis would be unlikely to be manually entered posthumously. I excluded those who had dementia in their CRIS records but were later diagnosed as having mild cognitive impairment (Petersen et al., 1999), as I judged this to mean these people had the dementia prodrome state rather than clinical dementia.

5.2.5 Analytic approach

I used the CRIS database record as the gold-standard definition of dementia because it includes records from the area's memory clinics, which are the principal UK dementia diagnostic services (Burns et al., 2014, Department of Health, 2009) in which people are assessed by trained psychiatrists in consultation with the broader clinical team. Those not seen in memory clinics would usually have been assessed by psychiatrists in other secondary mental healthcare services. Included patients were all assessed as part of routine clinical practice. They had all received an ICD-10 diagnosis of dementia (therefore fulfilling standardised gold-standard criteria) or another mental disorder during the study window. Though formal dementia screening assessment was not administered to all participants, dementia would likely have been considered as a differential diagnosis for people aged over 65 with psychiatric disorder, and those with suspicion of dementia would have received standard diagnostic work-up. I henceforth describe as 'sensitivity' the proportion of

people with dementia in CRIS who are correctly identified as having the condition in HES ('true positives'), and as 'specificity' the proportion of people without a dementia diagnosis in CRIS who are identified as such in HES ('true negatives').

A single cohort would not be adequate to analyse sensitivity and specificity because CRIS and HES assessments rarely take place simultaneously and for those with CRIS diagnosed dementia the date of onset is uncertain, and, for those without such a diagnosis at their last CRIS assessment, we could not be certain dementia did not develop later. Therefore, I analysed people with and without a CRIS dementia diagnosis separately. To assess sensitivity, I examined all HES records after the CRIS dementia index date which was the date of the first dementia diagnosis in the CRIS database, and up to 31st March 2016. For specificity, I examined all HES records from 1st January 2008 and before the CRIS 'index date', which was the date of last assessment in the CRIS database for people without dementia. All statistical analyses were undertaken using STATA 14.2 (2017).

5.2.5.1 Sensitivity of HES dementia diagnoses

I calculated:

1. Sensitivity of HES diagnosis for:

    a. each patient (proportion of people with dementia who have dementia recorded in any subsequent HES records).

    b. each admission (proportion of admissions of a person with dementia, after their index date, which have dementia recorded in HES).

    c. individual admission records for non-elective admissions only, because some patients have multiple repeated admissions for very short elective procedures, e.g. renal dialysis or chemotherapy, during which full diagnostic assessment is unlikely to have taken place.

2. Sensitivity of HES diagnosis for non-elective admissions within one year of diagnosis, stratified for year of admission, to evaluate time trends. I restricted this analysis to admissions within 1 year of CRIS dementia diagnosis as I aimed to ensure approximately equal dementia severity for each year in the study window. I judged that allowing a longer gap between CRIS and HES dementia assessment might bias findings due to ease of diagnosis of more severe dementia. I used chi-squared test to examine trend in sensitivity over time.

3. The association of marital status with the presence of dementia being correctly recorded in HES for each patient with dementia recorded in CRIS. I used logistic regression to calculate the odds ratio of true positive v false negative recording according to marital status adjusted for number of hospital admissions, then in models additionally adjusted for demographic characteristics (age, sex, ethnicity and socio-economic deprivation), then for clinical characteristics (MMSE score, HoNOS domains, dementia type). I present odds ratio of being a true positive v false negative according to marital status in sequentially adjusted models.

5.2.5.2 Specificity of HES dementia diagnoses

I calculated:

1. Specificity of HES diagnosis for:

    a. each patient (proportion of people without CRIS diagnosed dementia for whom dementia is absent in all preceding HES records.)

    b. each admission (proportion of admissions of a person without CRIS diagnosed dementia, before their index date, which have dementia absent in HES).

    c. specificity of individual admission records for non-elective admissions only.

2. Specificity for each non-elective admission of people without dementia, stratified for year of admission, to evaluate time trends. I did not include admissions after March 2015 to ensure all study participants had at least one year of potential CRIS follow-up after hospital admission. I used chi-squared test to examine trend in sensitivity over time.

3. The association of marital status with the absence of dementia being correctly recorded in HES for each patient without CRIS-recorded dementia. I used logistic regression to calculate the odds ratio of true negative v false positive recording according to marital status, adjusted for number of hospital admissions, then in models additionally adjusted for demographic characteristics (age, sex, ethnicity and socio-economic deprivation), then for clinical characteristics (MMSE score, HoNOS domains, dementia type). I present odds ratio of accurate recording according to marital status in sequentially adjusted models.

5.2.5.3 Additional analyses

There was missing data on at least one covariate for 27% of people with dementia and 61% of people without dementia. To avoid a loss of efficiency, I imputed missing covariate values using multiple imputation by chained equations (Oudshoorn et al., 1999). Five imputed datasets were created using STATA's *mi* package by replacing missing values with simulated values from a set of imputation models using a model constructed from all potential covariates and outcome variables. I conducted multivariable logistic regression on each imputed dataset and combined coefficients using Rubin's rules (Rubin, 2004).

5.2.6 Data use and ethics statement

I applied to the South London and the Maudsley NHS Foundation Trust CRIS oversight committee for permission to use the data included in this study. No specific ethical approval was required for my study; the Oxfordshire Research Ethics Committee C (reference 08/H0606/71+5) approved analyses of the CRIS database, including linked analysis of the HES data with a condition of oversight by the CRIS committee.

5.3 Results

The study sample comprised 21,387 people. Of these, 8,246 had dementia diagnosed in CRIS (South London and Maudsley) during the study period and 13,141 did not. The sociodemographic and clinical characteristics of the study sample and percentage of missing covariate data are summarised in Table 5-1, for people with recorded dementia in CRIS, and in Table 5-2 for those without dementia in CRIS data.

The mean age at dementia diagnosis was 82.2 years and 60.4% were female. For the people without dementia, mean age at index date was 77.9 years and 55.4% were female. The majority were from White ethnic background and African/Caribbean people formed the largest ethnic minority group. People in the sample were mostly married or widowed. Alzheimer's disease was the dementia subtype for around half of people with dementia and vascular dementia for a quarter. The median time between dementia diagnosis in CRIS and subsequent general hospital admission was 1.4 years (interquartile range (IQR) 0.5, 2.7 years) and the time between CRIS assessment of people without dementia and prior general hospital assessment was 1.7 years (IQR 0.6, 3.5 years).

Table 5-1: Socio-demographic and clinical characteristics of participants with dementia, according to whether dementia recorded in Hospital Episode Statistics (n=8,246)

		Dementia recorded in HES (n=6,429)		Dementia not recorded in HES (n=1,817)		p-value
		n	%	n	%	
Age at diagnosis	Mean (SD)	82.6 (6.8)		80.9 (7.4)		< 0.001
	65 – 69	272	9.0	163	4.2	
	70 – 74	675	13.3	241	10.5	
	75 – 79	1266	21.2	386	19.7	
	80 – 84	1720	25.5	464	26.8	
	85 – 89	1671	20.0	363	26.0	
	90+	825	11.0	200	12.8	
	Missing	*0*		*0*		
Sex	Female	3929	61.1	1053	58.0	0.01
	Missing	*0*		*1*		
Ethnicity	White	5019	78.1	1273	70.1	< 0.001
	Asian	274	4.3	107	5.9	
	Black	821	12.8	315	17.3	
	Other	189	2.9	86	4.7	
	Missing	*126*		*36*		
Marital status [a]	Married	2020	31.4	587	32.3	< 0.001
	Divorced	460	7.2	167	9.2	
	Widowed	2580	40.1	612	33.7	
	Single	1053	16.4	338	18.6	
	Missing	*316*		*113*		
Mean deprivation score (SD) [a]		27.2 (11.2)		27.8 (11.2)		0.04
	Missing	*0*		*0*		
Mean MMSE (SD) [a]		18.2 (6.2)		20.2 (5.9)		< 0.001
	Missing	*870*		*269*		
Problem with:	Agitation	1321	20.6	222	12.2	< 0.001
	Self-injury	78	1.2	23	1.3	0.82
	Alcohol / drugs	150	2.3	62	3.4	0.008
(from HoNOS subscale) [a]	Cognition	5647	87.8	1282	70.6	< 0.001
	Physical illness	3895	60.6	1109	61.0	0.34
	Hallucinations	787	12.2	187	10.3	0.04
	Depressed mood	731	11.4	248	13.7	0.005
	Relationships	1064	16.6	257	14.1	0.03
	Daily living	4390	68.3	1020	56.1	< 0.001
	Living conditions	733	11.4	226	12.4	0.14
	Occupation/activities	2141	33.3	505	27.8	< 0.001
	Missing [b]	*294*		*106*		
Last recorded dementia diagnosis	Alzheimer's disease	3373	52.5	796	43.8	< 0.001
	Vascular dementia	1461	22.7	390	21.5	
	Lewy body	201	3.1	54	3.0	
	Other dementia	443	6.9	133	7.3	
	Unspecified	951	14.8	444	24.4	
Median number of hospital admissions (I.Q.R.)		4 (2,6)		2 (1,3)		< 0.001

Table 5-2: Socio-demographic and clinical characteristics of participants without dementia, according to whether dementia recorded in Hospital Episode Statistics (n=13,141)

		Dementia not recorded in HES (n=12,094)		Dementia recorded in HES (n=1,047)		p-value
		n	%	n	%	
Age at last assessment	Mean (SD)	77.5 (8.2)		82.2 (7.8)		< 0.001
	65 – 69	2817	23.3	77	7.4	
	70 – 74	2390	19.8	122	11.7	
	75 – 79	2342	19.4	200	19.1	
	80 – 84	2069	17.1	244	23.3	
	85 – 89	1534	12.7	233	22.3	
	90+	942	7.8	171	16.3	
	Missing	*0*		*0*		
Sex	Female	6638	54.9	638	60.9	< 0.001
	Missing	*2*		*0*		
Ethnicity	White	9153	80.1	790	80.5	0.80
	Asian	597	5.2	44	4.5	
	Black	1232	10.8	108	11.0	
	Other	450	3.9	39	4.0	
	Missing	*662*		*66*		
Marital status [a]	Married	3620	33.5	253	27.1	< 0.001
	Divorced	1260	11.6	78	8.4	
	Widowed	3137	29.0	361	38.7	
	Single	2804	25.9	242	25.9	
	Missing	*1273*		*113*		
Mean deprivation score (SD) [a]		26.8 (11.7)		27.5 (11.4)		0.06
	Missing	*0*		*0*		
Mean MMSE (SD) [a]		24.2 (5.5)		20.4 (6.8)		< 0.001
	Missing	*6436*		*490*		
Problem with: **(from HoNOS subscale)** [a]	Agitation	1493	16.6	205	26.2	< 0.001
	Self-injury	655	7.3	29	3.7	< 0.001
	Alcohol / drugs	574	6.4	31	4.0	0.008
	Cognition	2503	27.9	444	57.8	< 0.001
	Physical illness	6253	69.4	613	78.5	< 0.001
	Hallucinations	1504	16.8	171	22.3	< 0.001
	Depressed mood	3408	37.9	252	32.6	0.003
	Relationships	1910	21.3	190	24.5	0.04
	Daily living	4413	49.3	5391	70.1	< 0.001
	Living conditions	1037	11.8	127	16.9	< 0.001
	Occupation/activities	2553	28.9	273	36.4	< 0.001
	Missing [b]	*3325*		*297*		
Median number of hospital admissions (IQR)		4 (2,8)		6 (3,11)		< 0.001

Key for Table 5-1 and Table 5-2: HES = Hospital episode statistics; HoNOS = Health of the nation outcome scale; IQR = Interquartile range; SD = Standard deviation
Notes for Table 5-1 and Table 5-2: [a] Characteristic nearest to first hospital admission; [b] Figure for missing HoNOS score is for the HoNOS domain with most missing information

5.3.1 Sensitivity of general hospital diagnoses of dementia

Of the 8,246 people with dementia who were admitted to hospital, 6,429 had dementia diagnosis at any time in their general hospital records, meaning that sensitivity = 78.0% (95% CI 77.1, 78.9) (Table 5-3). The 8,246 people had 37,329 total admissions following their dementia diagnosis during the study period and the proportion of the individual hospital records which included dementia was 50.3% (49.8, 50.8). Sensitivity for 26,894 non-elective hospital admission records was 63.3% (62.7, 63.9).

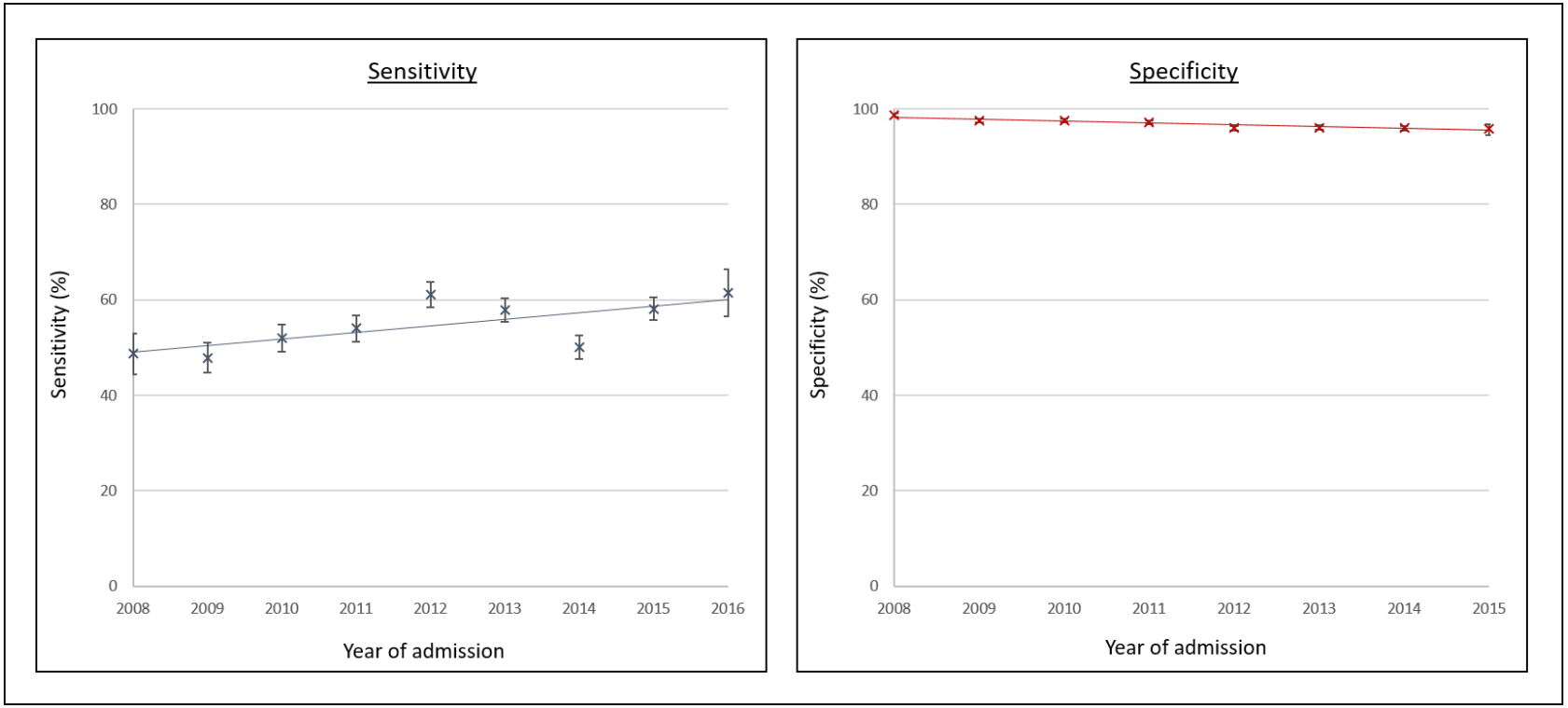
Table 5-3: Sensitivity and specificity of general hospital diagnoses of dementia 2008-16, for each individual patient and for each individual admission

	Number of true positives / total with dementia Sensitivity (95% CI)	**Number of true negatives / total without dementia Specificity (95% CI)**
For each patient	6,429 / 8,246 78.0% (77.1, 78.9)	12,094 / 13,141 92.0% (91.6, 92.5)
For each admission	18,769 / 37,329 50.3% (49.8, 50.8)	99,302 / 101,126 98.2% (98.1, 98.3)
For each non-elective admission	17,023 / 26,894 63.3% (62.7, 63.9) [a]	46,973 / 48,650 96.6% (96.4, 96.7) [b]

Notes: [a] Excludes 10,435 elective admissions; [b] Excludes 52,476 elective admissions

Sensitivity of general hospital records within 1 year of CRIS diagnosis increased from 48.7% (95% CI 44.3, 53.0) for admissions during 2008 to 61.5% (95% CI 56.5, 66.4) for admissions in 2016 ($p_{trend} < 0.001$ (chi squared = 87.7, 8 df)) (shown in Figure 5-1, with full data in Appendix 6).

Figure 5-1: Sensitivity and specificity of general hospital dementia diagnoses during non-elective general hospital admissions 2008-2016



Notes: Sensitivity figures are based on Hospital Episode Statistic (HES) dementia diagnosis during the specified year for non-elective admissions within one year of dementia diagnosis in Clinical Record Interactive Search (CRIS). Sensitivity figures are based on HES dementia diagnosis during the specified year for all non-elective admissions before the final CRIS assessment of a person not diagnosed with dementia.

In unadjusted analyses (Table 5-4), I found that being divorced, compared to married, was associated with lower odds of a person with dementia having it detected during subsequent general hospital admissions and being widowed was associated with higher rate of dementia recording. However, these associations did not persist when adjusted for demographic characteristics. In the model additionally adjusted for clinical characteristics, although marital status overall was not associated with the presence of dementia being correctly recorded in general hospital records of people with dementia (p = 0.17), there was some evidence that being single specifically, compared to married, was associated with lower odds of dementia recording (OR = 0.81 (0.67, 0.99)). The fully adjusted model using a multiply imputed dataset yielded similar pattern of results (Appendix 7), although single marital status was not significantly associated with dementia recording in multiply imputed data.

Table 5-4: The association of marital status with the presence of dementia being correctly recorded in general hospital records of people with dementia

		Married	Divorced	Widowed	Single
Unadjusted (n=8,246)	OR	1	**0.80 (0.66, 0.98)**	**1.23 (1.08, 1.39)**	0.91 (0.78, 1.06)
	p value		**0.03**	**0.002**	0.20
Model 1 [a] (n=7,817)	OR	1	**0.76 (0.62, 0.93)**	**1.25 (1.10, 1.42)**	0.93 (0.79, 1.08)
	p value		**0.008**	**0.001**	0.33
Model 2 [b] (n=7,776)	OR	1	0.84 (0.68, 1.04)	1.03 (0.89, 1.19)	0.86 (0.73, 1.01)
	p value		0.10	0.68	0.07
Model 3 [c] (n=6,037)	OR	1	0.89 (0.69, 1.14)	0.98 (0.82, 1.17)	**0.81 (0.67, 0.99)**
	p value		0.35	0.80	**0.04**

Key: OR = Odds ratio

Notes: [a] Model 1 = adjusted for number of hospital admissions; [b] Model 2 = adjusted additionally for age, sex, ethnicity and socioeconomic deprivation; [c] Model 3 = adjusted additionally for MMSE, HoNOS domains and dementia type. Bold figures indicate p<0.05 in multivariable analysis

5.3.2 Specificity of general hospital records of dementia

Of the 13,141 people who did not have dementia diagnosed by CRIS (South London and Maudsley) and who were admitted to hospital prior to their last contact, 12,094 did not have dementia entered at any time in their previous HES records, so specificity = 92.0% (91.6, 92.5) (Table 5-3). These 13,141 people had 101,126 admissions prior to their last CRIS assessment and the proportion of the individual HES records which did not include dementia was 98.2% (98.1, 98.3). Specificity in 48,650 non-elective hospital admission records was 96.6% (96.4, 96.7).

Specificity of HES dementia records has decreased slightly, with diagnostic specificity for admissions in 2006 being 98.7% (98.3, 99.0) and in 2015 being 95.8% (94.6, 96.8) (p_{trend}<0.001 (chi squared = 117.0, 7 df)) (Figure 5-1, with full data in Appendix 6).

Although 'true negative' v 'false positive' diagnosis was less likely for widowed and single people in unadjusted analyses, these associations did not persist following adjustment for socio-demographic characteristics (

Table 5-5). Marital status overall was not associated with recording of dementia in general hospitals in people without CRIS-diagnosed dementia (p=0.71). Similar results were found in my sensitivity analysis accounting for missing data using multiple imputation (Appendix 7).

Table 5-5: The association of marital status with the absence of dementia being correctly recorded in general hospital records of people without dementia

		Married	Divorced	Widowed	Single
Unadjusted (n=13,141)	OR	1	1.13 (0.87, 1.47)	**0.61 (0.51, 0.72)**	**0.81 (0.67, 0.97)**
	p value		0.09	**< 0.001**	**0.01**
Model 1 [a] (n=12,985)	OR	1	1.25 (0.97, 1.62)	**0.61 (0.52, 0.71)**	**0.78 (0.66, 0.93)**
	p value		0.08	**< 0.001**	**0.006**
Model 2 [b] (n=12,667)	OR	1	1.13 (0.87, 1.47)	0.93 (0.78, 1.10)	0.85 (0.71, 1.01)
	p value		0.36	0.38	0.07
Model 3 [c] (n=5,575)	OR	1	0.99 (0.69, 1.43)	0.95 (0.73, 1.25)	0.87 (0.66, 1.16)
	p value		0.68	0.84	0.39

Key: OR = Odds ratio

Notes: [a] Model 1 = adjusted for number of hospital admissions; [b] Model 2 = adjusted additionally for age, sex, ethnicity and socioeconomic deprivation; [c] Model 3 = adjusted additionally for MMSE and HoNOS domains; Bold figures indicate p<0.05 in multivariable analysis

5.4 Discussion

In this study examining the accuracy of general hospital records of dementia, I found that overall sensitivity and specificity of hospital dementia diagnoses were 78.0% and 92.0% respectively for each person's complete hospital records, and 63.3% and 96.6% respectively for each individual non-elective hospital admission. The rate of dementia diagnosis in HES is increasing over time, with admission-level sensitivity increasing from 48.7% in 2008 to 61.5% in 2016 and specificity decreasing from 98.7% to 95.8%. Having more hospital admissions was associated with higher rate of dementia recording, both 'true positive' and 'false positive'. I also found some evidence that missed diagnosis of dementia in general hospitals is more likely in people who are single compared to married, although other unmarried groups were not more likely to have diagnosis missed, and 'false positive' diagnosis was not associated with marital status.

5.4.1 Sensitivity and specificity

My study's estimate of general hospital record dementia diagnostic sensitivity is higher than those from previous studies which reported sensitivity to be between 26 and 70% (Dahl et al., 2007, Feldman et al., 2012, Jin et al., 2004, Knopman et al., 2011, Solomon et al., 2014). The wide variation in previous studies suggests that setting-specific factors are important. No previous study has examined UK records, so it may be that UK recording rate is higher than other countries as accurate diagnostic coding is incentivised due to it being linked to payment since 2005 (Farrar et al., 2009). Additionally, my novel finding of increasing general hospital recording of dementia over time may also partly explain the higher sensitivity in this study, as it is based on more recent data than any previous study; I used data to 2016, whereas no previous study had used data more recent than 2008. The observed increase in recording probably reflects increasing healthcare professional awareness of dementia,

increasing coding accuracy (Perera et al., 2016b, Burns et al., 2011) and greater communication between primary and secondary care. Furthermore, efforts in 2012 by the UK Department of Health to increase diagnosis rates in secondary care by case finding in older admitted people (Department of Health, 2012) may have also increased diagnosis in general hospitals, which is supported by my finding of increased diagnostic sensitivity during that year (Appendix 6).

The increasing rates of dementia recording are important as recognition of dementia during hospital admissions allows the clinical team to make appropriate adjustments to their communication style, incorporate family members views on healthcare decisions, initiate specific treatment for dementia's symptoms and consider the effects of dementia on management of other comorbid conditions.

My specificity estimate of 92% was lower than figures of 98% (Jin et al., 2004) and 99% (Dahl et al., 2007) from other studies. 'False positive' dementia diagnosis (i.e. diagnosis in HES when later assessment did not result in dementia diagnosis in CRIS) is a possible unintended consequence of the drive for earlier dementia diagnosis and potentially harmful. However, my analysis of specificity should be interpreted with caution and the true figure may in fact be higher. My analysis is based on a cohort of people in contact with secondary mental healthcare services who may be more likely than a general population to have symptoms resembling dementia. Furthermore, I reported in the published study on this topic (Sommerlad et al., 2018a) that older age, worse cognitive function and problem with daily living activities and agitation predicted 'false positive' recording of dementia and these are features are characteristic of dementia. Therefore, some of these may actually represent correct diagnosis of dementia in the general hospital and incorrect diagnosis (i.e. failure to detect dementia) by CRIS in which case the specificity is underestimated. Therefore, the evidence underpinning my findings related to specificity is less strong.

5.4.2 Effect of marital status on diagnostic recording

I found some evidence that single people with previously recognised dementia were less likely than married people with dementia to have the condition recorded in their

hospital records. This is consistent with previous research which found that 57% of people with dementia who cohabited had previously received the diagnosis, compared to 38% of those who lived alone (Wilkins et al., 2007), and another study which found that unmarried women were 4.6 times more likely to be undiagnosed than married men (Savva and Arthur, 2015). This finding is likely to be partly due to the absence of an informant with detailed knowledge of the patient's symptoms, meaning that collateral history is difficult for a clinician to obtain and diagnosis is therefore less certain. Previous findings of lower diagnosis rates in unmarried people may also be partly related to single people with dementia being less likely to access clinical services than a married person although, as I only examined people who had been admitted to hospital in this study, this cannot account for my results. This finding has potential implications for the use of electronic health records to ascertain dementia cases in Whitehall II, as there may be systematic bias in these data causing single people with dementia, and therefore possibly those who are less socially connected (Campbell and Lee, 1992), to be underestimated in electronic health records. If this is the case then it would result in underestimation of an association between social network contact and incident dementia.

However, in this study the overall association after adjustment between marital status and dementia recording was not significant, and I did not find that divorced or widowed people had a significantly lower rate of dementia recognition in hospital in this study, which I would expect if unmarried status were a marker of poor dementia recording. There was no significant association between marital status categories and dementia recording in model 2, which was only adjusted for socio-demographic characteristics, and the association for single people only emerged when adjusted for MMSE and HoNOS clinical features (model 3). These features may be confounders of the association and therefore should be adjusted for; e.g. psychiatric symptoms, substance use or poor cognitive status may affect both likelihood of marriage and diagnostic recording accuracy. However, they may also be along the causal pathway; marital status affects mood or substance use and this, rather than marital status per se, affects diagnostic recording. Therefore, the emergence of significant association between single status and diagnostic accuracy in model 3 should be interpreted with

caution. Of note, one other previous study examined the association between social functioning, which may be linked to marital status, and likelihood of dementia diagnosis being recorded and found no association (Valcour et al., 2000).

5.4.3 Strengths and limitations

This is the largest and most up-to-date analysis of hospital register dementia diagnoses, with sufficient data to allow the first analysis of changes in accuracy over time. I used a very large secondary care mental health register as gold-standard against which to test accuracy of general hospital diagnosis, with natural language processing used to increase the accuracy of my data by picking up people whose diagnosis had been written in text records, rather than in structured diagnosis fields.

Missed dementia in the CRIS record is however possible, even though it is based upon the assessment of trained psychiatrists from dementia services. I therefore restricted my sample to people over 65 years whom the mental healthcare service would have been likely to assess for dementia. As the CRIS data source is retrospective, I am not able to validate its accuracy by assessing participants, as used in other studies (Norton et al., 2016) as it would rely on information, in particular collateral history and cognitive examination, obtained and documented for individual patients. Records are likely to be written in a way that reflects the clinician's overall clinical impression so if I, as an independent researcher, reviewed these records, it is likely that my diagnostic judgement would reflect that of the original clinician. Missed dementia diagnosis in CRIS may mean that sensitivity in this study is overestimated – I expect that people with dementia whose condition was missed in CRIS would also be more likely to have missed diagnosis in HES – and that specificity may be underestimated, as described above (section 5.4.1).

National dementia recording rates are estimated to be around 68% and estimates for people in this study's catchment area are similar (75% overall) (NHS England, 2017), meaning that CRIS records will miss people with dementia because they have not presented to services. For individuals never seen in secondary mental healthcare services, therefore not in our CRIS cohort, HES diagnostic sensitivity may be worse as

they may be more likely to have characteristics associated with lack of HES dementia recording. Finally, our sample was derived from a specific region in urban and suburban London, which could limit representativeness. However this area has considerable ethnic and socio-economic diversity, which allowed me to examine the effect of these factors on dementia recording, and the hospital records were from all of England, so our results are likely to reflect a range of hospital diagnostic practice.

5.4.4 Clinical implications of general hospital dementia detection rates

UK efforts to increase dementia diagnosis rates in general hospitals have had success but there is lower recording rates in some groups, likely due to communication difficulties, lack of an informant, or the presence of other causes of cognitive decline. It is therefore important that clinicians are aware of this inequality, and that they have a higher index of suspicion in these patient groups. Policymakers should consider more targeted case-finding approaches and providing training for hospital clinicians in dementia detection in patient groups at risk of missed diagnosis. Better sharing of diagnostic information between healthcare providers, such as automatic population of hospital databases with previously diagnosed conditions, would increase clinician awareness of comorbid conditions including dementia. Future prospective research should seek to identify in more detail the effect of factors such as the presence of an informant on dementia diagnostic accuracy.

5.4.5 Implications for use of electronic hospital records in social network research

The findings from this study also establish the validity of hospital episode statistics as a tool for my future research. I found that, with median 2.5 years of follow-up after dementia diagnosis in secondary mental health-care services, around three quarters of people with dementia who were admitted to a general hospital had the condition entered in their inpatient electronic health records. This figure was higher than any previous study which has examined data from the US and Scandinavia, suggesting that UK HES records may be more accurate than records from these settings. These data were more recent than other records, with data accurate to March 2016 and I note the important dynamic of increasing accuracy of dementia records over the past

9 years. The Whitehall II linked electronic health record data are accurate to March 2017, which means that this data are likely to benefit from the improvements in diagnostic recording over time. Having more hospital admissions over time, and dementia being more severe increased the chance of dementia being recorded, suggesting that longer duration of follow-up from time of diagnosis is another important factor which contributes to data accuracy.

In this study, there was some evidence that single people with dementia admitted to hospital were less likely to have dementia recorded than married people with dementia in hospital. This suggests that there may be systematic bias in routine diagnostic practice meaning that electronic health records underestimate dementia in single people. The association was of borderline statistical significance and one previous study has not found this association (Valcour et al., 2000). However, this finding is consistent with two other studies (Wilkins et al., 2007, Savva and Arthur, 2015), and with findings from my systematic review that studies using clinical registers found the association between unmarried status and incident dementia to be lower than studies which clinically examined each participant (Sommerlad et al., 2018b).

However, this study only examined rates of dementia recognition in people who were already admitted to hospital. When specifically considering hospital inpatient record accuracy, we need to consider differences in hospital admission rates and it is plausible that unmarried people are more likely to be admitted to hospital as they lack a spouse able to care for them at home, or that admission is less likely as they do not seek medical attention. Evidence from my own research and previous studies suggests this to be the case. In my research using this data I found that during 2.5 years median follow-up, 75.9% of people with dementia from South London and Maudsley CRIS were admitted to a general hospital (Sommerlad et al., 2019) (Appendix 8). Although analyses were not statistically significant, there was some evidence that people who were unmarried were more likely to be admitted to hospital (single vs married adjusted incidence rate ratio (IRR) = 1.10 (0.98, 1.23); divorced vs married IRR 1.13 (0.97, 1.30); widowed vs married IRR = 1.10 (1.00, 1.21)).

While two other studies did not find association between living alone (n = 677) or marital status (n = 827) and hospitalisation (Nourhashemi et al., 2005, Rudolph et al., 2010), a French study of 1,131 people with dementia found those living alone at higher risk of hospitalisation than people who cohabited (RR = 1.33 (1.01, 1.74), adjusted for differences in physical health) (Soto et al., 2015). Higher admission rates in unmarried people may therefore compensate to some extent for the reduced sensitivity of inpatient hospital records in these groups.

My study examined inpatient dementia records, but Whitehall II derives its data from three different electronic health record data sources, covering inpatient, outpatient and mortality data. One US study of data to 2000 reported outpatient records to be highly accurate with positive predictive value (PPV), meaning the proportion of cases identified by the outpatient record which were correctly identified as having dementia, of 86% (Pippenger et al., 2001). A more recent UK study of data up to 2012 reported PPV of combined inpatient and outpatient records to be 85% (Brown et al., 2016). There are varying estimates of the sensitivity of death certificates for dementia diagnosis, ranging from 21% to 65% (Wilkinson et al., 2018). Two UK studies have examined this area, finding sensitivity to be 65% in a 1993 study (Newens et al., 1993), and 54% in a linked health record study of data from 2006 to 2013, with this study also finding increasing levels of death certification over time (Perera et al., 2016b). Neither of these studies examined whether premorbid marital status, living status or social network contact affected death certification of dementia.

5.4.6 Conclusions relating to use of electronic health records in Whitehall II study

Deriving data from multiple different data-sources has been shown to increase the ascertainment of dementia in electronic records (Wilkinson et al., 2018). Sensitivity of dementia diagnosis in hospital data alone was 40% in one study but this increased to 62% when hospital and mortality data were used (Feldman et al., 2012) and sensitivity was 43% in hospital records and 52% in combined hospital and mortality data (Jin et al., 2004). Therefore the use of three data sources in Whitehall is likely to improve detection of dementia. In previous research using the Whitehall cohort, all

three databases were a source of dementia cases; 53% were first recorded in the hospitalisation data, 44% in the mental health register and 2% in mortality data. While multiple data sources improve ascertainment, it is unclear whether this would ameliorate the potential systematic bias in rates of detection in people who are unmarried or have less frequent social network contact, or whether this problem may simply be amplified by adding other data sources. If such measurement bias persists, then it would result in underestimation of any protective effect of social contact with dementia.

The current UK estimate of national dementia diagnosis rate is 68% (NHS Digital, 2018), based upon the proportion of the number of people with dementia entered in their general practice record compared to the number estimated to have dementia using UK prevalence data (Matthews et al., 2013). The data used by Whitehall to derive dementia cases cover all potential national databases derived from UK clinical practice, except from primary care data. However, dementia is infrequently diagnosed solely in primary care settings as national guidelines recommend referral to specialist care, rather than general practitioner diagnosis (Pink et al., 2018). This is supported by a UK study which compared HES data with general practice data, finding that in 866 people without dementia in HES, only one was reported by the general practitioner to have dementia; suggesting that, for dementia ascertainment, primary care data are likely to add very little to other routine data-sources (Brown et al., 2016). It is therefore likely that dementia ascertainment rates in the three databases used by Whitehall II would approximate the national estimate of 68%.

It should also be noted that using routine data to ascertain cases confers significant advantages to data collection for epidemiological studies. This approach avoids the cost of clinical examination of all study participants and makes it possible to obtain follow-up data on all study participants, thereby reducing attrition bias which would likely result in loss of people at highest risk of developing dementia (Brilleman et al., 2010). Therefore, I judge it is acceptable to use electronic health records as a source of dementia ascertainment in my subsequent research, with consideration given to the potential limitations, which may reduce the size of any association.

Chapter 6: **Association of social contact frequency with risk of dementia and cognitive decline**

6.1 Introduction

There is need to identify modifiable risk factors as targets for dementia prevention strategies as the ageing population is expected to lead to rising numbers of people living with dementia (Ahmadi-Abhari et al., 2017). As discussed in section 2.3, frequent contact with others has been suggested to confer protection against dementia (Livingston et al., 2017), possibly by building cognitive reserve therefore increasing resilience against neuropathological damage and delaying dementia onset (Stern, 2012). Previous meta-analyses of longitudinal studies found less frequent social contact to be associated with greater risk of dementia (Kuiper et al., 2015) and cognitive decline (Kuiper et al., 2016), which is the characteristic feature of dementia. This finding is, however, susceptible to reverse causation bias due to the short duration of follow-up in most included studies, as discussed in detail in section 2.3.2. Infrequent social contact could therefore be a consequence of the dementia prodrome, rather than a cause of subsequent dementia.

In this chapter, I therefore aim to examine whether social contact frequency, measured at sufficient time before dementia onset to reduce likelihood of reverse causation, affects risk of incident dementia and cognitive decline. I chose to examine social contact frequency rather than any of the other domains of social relationships described in section 2.2 for several reasons. Firstly, previous associations have been found with this domain, rather than with size or availability of social network contacts (Kuiper et al., 2015). Secondly, it is viewed as the most objective measure of social relationships (Valtorta et al., 2016). Thirdly, if social contact confers health benefits then greater frequency would be expected to be beneficial. As discussed in section 2.3.2, using data which permits examination of different aspects of social contact, e.g. with friends or relatives, is advantageous as putative protective associations, and the nature of prodromal changes, may differ between these groups. Data with

repeated measures of social contact allow for detailed examination of the consistency of association of social contact throughout the life-course with cognitive outcomes and of the potential for prodromal changes by examining whether change in social contact in old age is strongly associated with dementia incidence.

6.1.1 Selection of cohort

I sought suitable cohorts by examining cohort profile papers, and websites listing cohorts - the Medical Research Council and Dementia Platforms UK cohort directories (Medical Research Council, 2019, Dementia Platforms UK, 2019). I aimed to find large cohorts with 1) multiple measurements of frequency of contact with friends and relatives over follow-up of at least 10 years, which would be longer than any previous study examining this association and previous studies have suggested that this duration of follow-up is required to reduce risk of reverse causation bias (Singh-Manoux et al., 2017, Amieva et al., 2008, Kivimäki et al., 2018); 2) detailed measurement of potential covariates; 3) ascertainment of dementia and cognitive status; and 4) a study population with a large proportion of older (i.e. over 75 years) participants at risk of dementia by the end of follow-up.

I chose to use the Whitehall II cohort (Marmot and Brunner, 2005) for this study as it meets these criteria. I also identified that the Longitudinal Aging Study Amsterdam (Huisman et al., 2011) had measured social contact consistently over a slightly shorter duration and I plan to examine the replicability of the findings of this chapter in this cohort in future. Other large UK studies of older people were less suitable for this analysis. The English Longitudinal Study of Aging (ELSA) and Cognitive Function and Aging II study (CFAS-II) had shorter duration of follow-up (Steptoe et al., 2012, Matthews et al., 2013). The 1946 national birth cohort (MRC National Survey of Health and Development (NSHD)) had fewer very old participants (Wadsworth et al., 2005). In addition, ELSA and NSHD asked on fewer occasions about social contact, and the measures used evaluated combined contact with friends and relatives, rather than allowing separate examination of these different social contacts.

6.1.2 Aims and objectives

My overall aim of this study was to examine the influence of frequent social contact during the life-course on the risk of developing dementia and cognitive decline. My specific objectives were to:

1. test the association between frequency of social contact with friends and relatives at 50, 60, and 70 years of age and incident dementia
2. examine association between change in social contact and incident dementia
3. examine the association between social contact and subsequent cognitive decline

6.2 Methods

6.2.1 Study design and participants

Data for this study are drawn from the Whitehall II study (Marmot and Brunner, 2005), an ongoing prospective cohort established in 1985. The original target population was all civil servants working within the London offices of 20 departments of the UK civil service, including people from clerical and support grades, middle-ranking executive grades and senior administrative grades, aged between 35 and 55 years. The response rate from those invited to participate was 73% (74% for men and 71% for women) (Rael et al., 1995).

6.2.1.1 Consent and ethical approval

Written, informed consent for participation was obtained at each study contact. Ethical approval has been granted for each phase of the study, with most recent approval by the Joint University College London/University College London Hospitals Committee on the Ethics of Human Research (Committee alpha; reference 96/0938).

6.2.2 Measurements

Participants filled in questionnaires at each of the 12 waves of data collection which have been completed to date – further study phases are planned. Participants additionally underwent a structured clinical evaluation including biological, clinical

and cognitive measurements at 5 yearly intervals during alternate waves. Figure 6-1 shows the waves and collection of social network and cognitive data which I used in my analyses. These were data from phase 1 (1985-88), phase 2 (1989-90), phase 3 (1991–94), phase 5 (1997–99), phase 7 (2002–04), phase 9 (2007-09), phase 11 (2012–13), and phase 12 (2015-16).

Figure 6-1: Summary of Whitehall II study data collection schedule and participant numbers

Phase	Year	Number of participants	Mean Age (y)	Social contact	Cognitive function	Dementia cases
1	1985-88	10,308	44.9			
2	1989-90	8,132	47.9			
3	1991-94	8,815	50.3			
4						
5	1997-99	7,870	56.0			
6						
7	2002-04	6,967	61.2			
8						
9	2007-09	6,761	66.0			
10						
11	2012-13	6,318	69.8			
12	2015-16	5,632	72.6			

6.2.2.1 Social network contact

Social network contact was assessed on six occasions (phases 1, 2, 3, 5, 7 and 11). Participants completed, by self-completed questionnaire, four ordinal self-rated questions taken from the Berkman/Syme social network index (Berkman and Syme,

1979). These questions enquire about the frequency of contact with friends and relatives and the number of friends and relatives seen at least monthly. They therefore measure frequency of social contact, implicated in previous research to have association with dementia (Kuiper et al., 2015). These questions, their response options and scoring are summarised in Figure 6-2. I generated social network contact variables by combining responses from the four questions (on scale 0-16), and the two questions about contact with friends (0-8), and relatives (0-8).

Figure 6-2: Measurements of social contact used in Whitehall II study

	Question	Response options	Scoring
Friends	**1)** Do you have any friends or acquaintances you visit or who visit you? (Not necessarily the same person each time)	Never/almost never	0
		Once every few months	1
		About monthly	2
		About weekly	3
		Almost daily	4
	2) How many friends or acquaintances do you see once a month or more?	None	0
		1-2	1
		3-5	2
		6-10	3
		>10	4
Relatives	**3)** Are there any relatives outside your household whom you regularly visit or who visit you? (Not necessarily the same person each time)	Never/almost never	0
		Once every few months	1
		About monthly	2
		About weekly	3
		Almost daily	4
	4) How many relatives do you see once a month or more?	None	0
		1-2	1
		3-5	2
		6-10	3
		>10	4
Total score			**0-16**

6.2.2.1.1 Psychometric properties of the social contact measure

There are no studies of the psychometric properties of the measures specifically used in Whitehall II, but many similar scales used in other studies have undergone psychometric evaluation and found to have acceptable properties, which I discuss below.

6.2.2.1.1.1 Reliability

Questions about frequency of contact with friends and relatives in a Swedish longitudinal cohort had test-retest correlation of r = 0.66 and r = 0.76 respectively (Helminen et al., 1995). Other studies have found higher correlation: the Interview Schedule for Social Interaction measuring availability of social interaction, reflecting social network contact, had test-retest reliability (r = 0.75) (Henderson et al., 1980). Another scale measuring social contact with friends and relatives had very high test-retest reliability (r = 0.91) (Wasserman and Faust, 1997). A further scale, the Interview Measure of Social Relationships which measures structural aspects of social contact, had test-retest reliability for social contact over 4 months of r = 0.73 (Brugha et al., 1987). I found that people with mild dementia can rate their own social functioning using a scale I devised, with high test-retest reliability (ICC = 0.80) (Sommerlad et al., 2017), suggesting that measurement of social contact continues to be reliable even when a participant starts to be cognitively impaired.

Some studies have suggested an acceptable threshold for test-retest reliability of 0.7, but others suggest that this should be adapted according to the measure used (Crocker and Algina, 1986). These values are likely to be acceptable considering that some variation in contact frequency with friends is to be expected. I will use multiple longitudinal measures of social contact which may help reduce the effect of measurement error.

The Interview Schedule for Social Interaction (Eklund et al., 2007) had acceptable internal consistency (α = 0.71). However, other studies have found that different aspects of social contact are not closely related – correlation between contact frequency with friends and relatives was low (r = 0.23) (Helminen et al., 1995) – which supports the need to examine friend and relative contact separately, in addition to in combination.

6.2.2.1.1.2 Validity

As discussed in section 2.2.2, there are no gold-standard ways of measuring social contact which would be acceptable and feasible, so testing construct validity of social

contact measures is challenging. Studies examining this area have found, in a clinical population with mean age 39 years, the Interview Schedule for Social Interaction to have construct validity – correlation with Global Assessment of Functioning (Endicott et al., 1976) by a researcher was r = 0.37 – and discriminant validity as scores differed between healthier and more unwell participants. As may be expected, a cohort study found those cohabiting with their partner had a larger mean social network than single people who lived alone (men 14.5 v 7.8, women 14.3 v 12.1) (van Tilburg, 1995).

The findings I previously outlined (sections 2.2.3 and 2.3) on the associations between social contact and health outcomes further support the predictive validity of social contact measures in research settings. Specifically, the study reporting the development of the Berkman-Syme index found an association between low level of social contact and increased mortality risk (Berkman and Syme, 1979). Research examining social contact in the Whitehall II study reported that low social contact predicts increased cardiovascular mortality (Stringhini et al., 2012). And, in a study I co-authored (Elovainio et al., 2017b), we found that people with a higher level of social contact frequency and those who were married were more likely to have a better subsequent cognitive trajectory. I will discuss differences between the current study and this previous study in more detail in section 6.4.9.2.1.

6.2.2.2 Dementia diagnosis ascertainment

Dementia diagnosis in Whitehall II is derived from comprehensive linked electronic health records using three databases; NHS Digital's Hospital Episode Statistics (HES) and the Mental Health Services Data (MHDS), and the mortality register (Health and Social Care Information Centre, 2017). I have described the HES dataset in detail in section 5.2.1.2. In addition to the inpatient records I used in my study described in chapter 5, Whitehall II uses HES data derived from outpatient and Accident and Emergency departments. HES and MHDS include clinical diagnoses recorded during routine clinical contact in inpatient, outpatient and community-based care in any English NHS service including memory clinics, the primary dementia diagnostic service in the UK (Burns et al., 2014). Diagnoses are entered as ICD-10 (World Health

Organisation, 2004) codes with F00x-F03x, F05.1 and G30x-G31.0 indicating dementia of any subtype. Diagnosis of specific dementia subtypes are often inaccurate or missing in routine clinical practice, as I discussed in section 2.1.2.1, so I chose to assess all-cause dementia rather than specific dementia subtypes.

6.2.2.2.1 Validity of dementia diagnoses in Whitehall II study

As I reported in section 5.4.5, HES records have sensitivity 78% and specificity 92% for dementia diagnosis, with increasing sensitivity observed over the past ten years (Sommerlad et al., 2018a). Systematic review data indicate that consolidation of multiple different data sources increases sensitivity (Wilkinson et al., 2018). The three datasets used for dementia ascertainment in Whitehall II are likely to give almost complete coverage for cases of dementia diagnosed in England, with the current diagnosis rate nationally estimated to be 68% (NHS Digital, 2018). There is evidence that dementia may be underestimated in clinical register data in unmarried people (Sommerlad et al., 2018a, Sommerlad et al., 2018b, Wilkins et al., 2007, Savva and Arthur, 2015), who may have lower level of social contact. However, there is also some evidence that those with smaller social networks, by living alone (Soto et al., 2015) or being unmarried (Sommerlad et al., 2019), are more likely to be admitted to hospital, a potential setting for dementia diagnosis; this may therefore compensate to some extent for reduced diagnosis rates in unmarried people.

The evidence regarding the validity of dementia cases in Whitehall II is strengthened by the finding of accelerated cognitive decline in Whitehall II study participants who later are diagnosed with dementia during the prodromal period, consistent with that in other studies (Singh-Manoux et al., 2017). Cognitive trajectories diverged, between dementia cases and those who did not develop dementia, 12 years before diagnosis. In my analysis, as I discuss in detail in section 6.3.8, cognitive trajectories differed between those with and without dementia, such that overall mean cognitive decline was nearly three times faster in those who developed dementia than those without, further supporting the validity of the use of these data.

6.2.2.3 Cognition

Cognitive tests were administered to all participants during clinical examination in phases 5, 7, 9, 11 and 12 (Figure 6-1), approximately 5 yearly. The cognitive test battery administered at each of these phases consists of measures of three cognitive domains:

1. Verbal fluency assessed by asking participants to recall in writing as many words beginning with 'S' (testing phonemic fluency) and as many animals (semantic fluency) as possible during 1 minute for each test. I summed the total number of correct words from these two verbal fluency tasks.
2. Short term verbal memory assessed by presenting participants with 20 one or two syllable words at 2 second intervals and testing recall in writing 2 minutes later. The score on this test was the number of words correctly recalled (maximum 20).
3. Verbal and mathematical reasoning assessed using the Alice Heim 4-I (AH4) test of 65 items of increasing difficulty completed during 10 minutes (Heim, 1967). Score out of 65 was used for this test of reasoning.

Other cognitive tests were also administered to participants but not at all phases, limiting the usefulness of these in examining cognitive change. The mini-mental state examination (Folstein et al., 1975) was used at phases 7, 9, 11, 12, not at phase 5. This test has limited sensitivity to change and there is a notable ceiling effect in healthy participants (Gluhm et al., 2013). The Mill Hill vocabulary test was administered at phases 5, 7, 9, 11 but not phase 12 and this test has also been shown to be insensitive to change as vocabulary is relatively well-preserved compared to other cognitive domains (Hartshorne and Germine, 2015). I therefore did not use either of these tests in my analyses.

As has been done in previous studies using these data (Elovainio et al., 2017b, Singh-Manoux et al., 2012) and in studies of other cohorts (Moller et al., 1998, Arvanitakis et al., 2004, Bennett et al., 2006a), I standardised all raw test scores to z-scores with mean = 0, standard deviation = 1. This approach has the advantage of reducing measurement error from individual tests and allowing easy comparison between

tests with different score ranges. I standardised the scores of each of the three tests based on the mean and standard deviation of phase 5 data. I then generated a global cognitive test z-score for each phase by summing and re-standardising these scores.

6.2.2.3.1 Psychometric properties of cognitive measurements

These tests have previously been found to be have good test-retest reliability in 556 Whitehall II participants who completed the tests twice within 3 months in the 1997-99 phase (r for each test ranged from 0.60 to 0.89) (Sabia et al., 2017). They have previously identified cognitive changes in people aged 45 years and older and differentiated between those with different levels of education (Singh-Manoux et al., 2012). Similar measures are used in other studies (Wadsworth et al., 2005).

The verbal fluency test had moderate test-retest reliability over 1 month in one study (*r* = 0.56 for animals, 0.63 for s-words) (Bird et al., 2004) and higher reliability in another (*r* = 0.68 for animals and 0.83 for s-words) (Harrison et al., 2000). There has previously been evidence of a small practice effect (Harrison et al., 2000), whereby scores increased slightly between assessments separated by 1 month (mean 23.4 animals at first assessment and 24.7 at second) (Bird et al., 2004).

Similar verbal memory tasks had moderate test-retest reliability over mean 47 days (r = 0.74) and a possible small practice effect (Benedict et al., 1998). Convergent validity was established as scores differed between healthy older people and those with dementia, (Shapiro et al., 1999) and predictive validity as poorer performance was associated with subsequent Alzheimer's dementia (Knopman and Ryberg, 1989). Scores on the Alice Heim test of reasoning are associated with measures of intelligence (Gold et al., 1995), were reliable between successive study waves in one study (r = 0.86) (Whitley et al., 2012), and have been shown to be sensitive to cognitive change (Singh-Manoux et al., 2012).

6.2.2.4 Potential covariates

I obtained sociodemographic characteristics of participants at each study phase. Age, sex, ethnicity (white, other ethnicity) and level of education (no formal education,

lower secondary, higher secondary education, graduate, postgraduate) were derived from the first study phase. Other characteristics were recorded at all study interviews. Adult socioeconomic status was estimated from the grade of last employment, categorised based upon the Registrar General's social class groupings (Szreter, 1984) (professional, managerial, skilled non-manual, skilled manual, partly skilled, non-skilled). Employment status (employed, not working (i.e. unemployed or retired) and marital status (married, divorced, widowed, lifelong single) were also recorded at each study phase.

Health behaviours were assessed at all phases: smoking (never smoked, ex-smoker, current smoker), alcohol consumption (0, 1-14, >14 alcoholic units per week), physical activity (hours of moderate or vigorous exercise per week). I also obtained data on mental health symptoms using the General Health Questionnaire (GHQ-30) (Goldberg, 1972).

6.2.3 Statistical analysis:

6.2.3.1 Data acquisition and management procedures

This study is a secondary data analysis of existing cohort study data. After gaining approval from the Whitehall II study committee and agreeing collaboration and supervision from Archana Singh-Manoux, study principal investigator and lead of the cognitive ageing programme of the Whitehall II study, I completed a data specification request form detailing the variables I required.

I undertook several data management tasks to prepare data for analysis. Questions 1 and 3, relating to social contact frequency were scored with higher score indicating less frequent social contact so I reversed the scoring of these variables. In phase 1, 2,596 study participants answered question 1 but not 2, for reasons which are unclear. These participants had provided a full range of question 1 responses, there was no instruction to skip question 2, and there was no similar pattern of missing data at subsequent waves, suggesting that data was missing completely at random. To minimise the impact of missing data, I imputed values for these responses. There was moderate correlation between question 1 and 2 responses for participants who

had answered both in phase 1 (Spearman's rank correlation = 0.54, p<0.001). I therefore chose to impute the mean question 2 response based upon participants' question 1 response for use in all analyses (Question (Q) 1 = 0, Q2 = 0.83; Q1 = 1, Q2 = 1.42; Q1 = 2, Q2 = 1.89; Q1 = 3, Q2 = 2.42; Q1 = 4, Q2 = 2.81). I conducted sensitivity analyses examining the effect of this imputation, which I will detail in section 6.2.3.3. I then combined social contact variables at each study phase into variables describing contact with friends (sum of questions 1 and 2), relatives (3 and 4), and friends and relatives (1 to 4).

For outcome data, I checked dates of diagnosis for those diagnosed with dementia to ensure they were within the study timescale and for cognitive data, I generated z-scores as described in section 6.2.2.3. I categorised covariate data as detailed in section 6.2.2.4 and, in order to minimise the effect of missing covariate data on adjusted analyses, I imputed missing data from the adjacent study phase, prioritising the measure at the previous study phase.

The study participants ranged in age from 35 to 55 at study inception, meaning that measurements at each study phase were of participants with a wide range of ages. To aid interpretation of my results, I therefore planned to present my primary results by age, rather than study phase. I generated variables for exposure and covariate data at age 50, 60, and 70 years, allowing a margin of +/- 5 years, by extracting the data from the phase closest to these ages. The 5 year margin meant that data from the same study phase was not used at successive age points.

6.2.3.2 Descriptive statistics

I described the socio-demographic characteristics of the cohort and whether these differed according to dementia status and baseline social contact, using t-test and ANOVA for continuous variables and chi-squared test for categorical variables. I described social contact with friends and relatives, combined and separately, at age 50, 60, and 70 years and change in social contact between age 60 and 70 years, and distribution of these variables. I analysed the correlation of social contact with friends and relatives at each age point and the correlation between social contact at

successive age points using Pearson's correlation coefficient. I described the number of cases of dementia and time from study inception to dementia diagnosis. I also described the raw cognitive scores (pre-standardisation) at each study phase and correlation between the three cognitive measures and the combined cognitive measures at successive measurements. I examined the distribution of covariates and log-transformed the physical activity variable for analyses as it was highly positively skewed.

6.2.3.2.1 Attrition and missingness bias

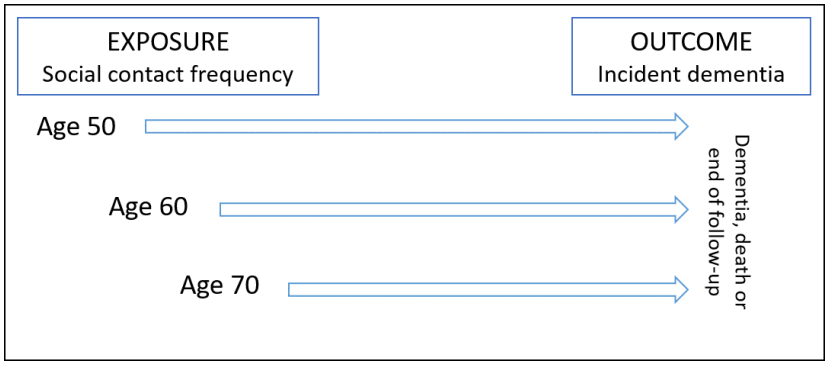
To assess attrition bias, I examined the association of participation in successive waves of data collection in the study according to key sociodemographic characteristics (age, sex, marital status), social network contact, and dementia status. To examine the potential effect of missing exposure variables, I examined whether subjects with missing or incomplete data on social contact at each age point differed from subjects with complete social contact histories on any of the covariates or on social contact at baseline (if recorded) or dementia status. I also considered whether missing cognitive function data at each study phase was associated with sociodemographic characteristics, social contact and dementia status. For these analyses, I used chi-squared test for categorical variables, and independent samples t-tests for continuous variables.

6.2.3.2.2 Covariates

To assess potential for confounding and describe bivariate relationships, I examined whether potential covariates were associated with social contact frequency and incident dementia. I also considered previous literature on associations between potential covariates and social contact and dementia. I planned *a priori* to treat age, sex, ethnicity, and education as covariates as these have consistently been linked to dementia incidence (Hofman et al., 1991, Plassman et al., 2007, Gao et al., 1998, Meng and D'Arcy, 2012, Adelman et al., 2011, Ng et al., 2010). I drew an acyclic directed graph (DAG) (Shrier and Platt, 2008) using www.dagitty.net (Textor et al., 2016) to describe relationships between variables and inform choice of covariates. I

discuss my choice of covariates in section 6.3.5, where I also show the DAG (Figure 6-4).

6.2.3.3 Association between social network contact at 50, 60, and 70 years and incident dementia



I used Cox regression (Cox, 1972) to model the association of social network (combined friend and relative contact; friend contact only; relative contact only) at age 50, 60, and 70 years with subsequent incident dementia, with age as the timescale. I used Cox regression as it analyses time to outcome event (dementia diagnosis), therefore handling varying lengths of observation between subjects, unlike logistic regression which examines the outcome as dichotomous. For each analysis, participants at risk of developing dementia were included (i.e. those without existing dementia who were still alive) and censoring occurred at date of dementia diagnosis, death, or 31st March 2017 (end of linked electronic health record data), whichever came first.

I examined the assumptions of the Cox regression model, by considering whether the ratio of hazards was proportional over time by 1) observing Kaplan-Meier plots and 2) examining Schoenfeld residuals (Schoenfeld, 1982). I tested whether the association between social contact and dementia was linear by examining locally weighted scatterplot smoothing (LOWESS) plots (Hess, 1995).

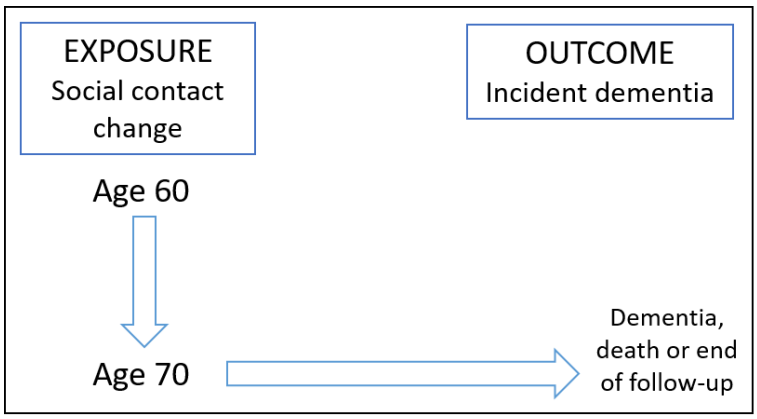
As I will describe in section 6.3.5, all results are presented as unadjusted; adjusted for birth cohort (using 5 year categories) and sex; and then with serial addition of ethnicity, education, socioeconomic status; smoking status, physical activity, and

alcohol consumption (health behaviours); whether still in employment; and marital status. Age, sex, ethnicity, and education are taken from baseline; socioeconomic status, health behaviours, employment and marital status are taken from time of exposure measurement.

I present hazard ratios for dementia according to one standard deviation increase in social network score. I examined for interaction between social network contact and age, sex, or marital status in the association with dementia using a likelihood ratio test and found no evidence of interaction (p=0.28, 0.48, and 0.99 respectively) so did not analyse by subgroups. I had also previously found no evidence that the association between marital status and dementia incidence varied according to sex of the subject (section 4.3.2.2).

The analyses of social contact at age 50, 60, and 70 years and subsequent dementia was based on 8,483, 7,348, and 4,870 participants respectively due to non-participation, and missing data. As I will describe in section 6.3.4, non-participation was associated with demographic characteristics, social network contact and incident dementia, so there was risk of attrition and missingness bias. Therefore, as my primary analysis I used inverse probability weighting (Seaman and White, 2013) to provide estimates having taken account of the likely impact of non-participation and missing data. I calculated the probability of inclusion in fully adjusted models at each age, using data on socio-demographic and behavioural factors, social network contact, dementia status and the interaction between social contact and dementia. I then used the inverse of these probabilities to weight the data. In sensitivity analyses, I also calculated unweighted associations.

6.2.3.4 Association between change in social network contact and incident dementia

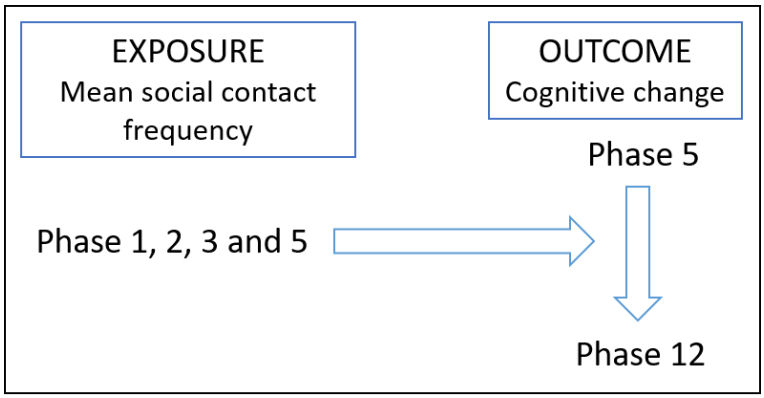


I examined social contact change, to consider in more detail than before whether reverse causation underlies associations between social contact and dementia. I examined the association between change in social contact from age 60 to 70 years and incident dementia using Cox regression, censored at date of dementia diagnosis, death, or 31st March 2017, whichever came first. I generated social change variables by subtracting social contact score at 60 years from score at 70 years, so a positive value indicated increase in social contact score. I then used this score as the exposure variable in models in which I adjusted sequentially for birth cohort (using 5 year categories) and sex; ethnicity, education and socioeconomic status; smoking status, physical activity, and alcohol consumption (health behaviours); employment; and marital status. Covariates were as measured at age 70 years. In all models, as I wanted to examine the effect of social change irrespective of preceding social contact, I also adjusted for social contact frequency at age 60 years. As described in section 6.2.3.3, I used inverse probability weighting to weight analyses for the probability of participants being included in these models.

To examine the association of social contact change and incident dementia in more detail, I also generated categories of social change from tertiles of social network contact at age 60 years and 70 years. Remain low = low at 60 and 70 years; remain medium = medium at 60 and 70 years; remain high = high at 60 and 70 years; increasing = change from low at 60 to medium or high at 70 years or from medium at 60 to high at 70 years; decreasing = change from high at 60 to medium or low at 70

years or from medium at 60 to low at 70 years. I then calculated the association between these five categories (with 'remain high' as reference group) and incident dementia after age 70 years, adjusted and inverse probability weighted as above, using covariates measured at 70 years.

6.2.3.5 Association between social contact and subsequent cognitive change



I used mixed linear models (Laird and Ware, 1982) to examine the association between social contact and subsequent cognitive change. I used these models as they allow examination of change in outcome with varying time between, and variable number of, outcome measurements. They also take into account the correlation between repeated measurements in individuals. Furthermore, they make use of all repeated measurements over follow-up and allow for missing data.

Cognition was tested at phases 5, 7, 9, 11, and 12, so I used measurements of social contact frequency preceding this (phases 1, 2, 3, 5). I calculated the mean of social contact scores during all these phases to reduce the effect of measurement error, and characterise social contact over a prolonged period of time – the mean 10 years between phase 1 and 5. From this variable, I generated tertiles of approximately equal size to use as the exposure variable in this analysis, comparing cognitive change according to preceding low, medium, and high social contact. I used the standardised z-scores as described in section 6.2.2.3 to examine combined cognition, verbal fluency, verbal memory and reasoning.

I first examined the mean rate of change in the z-scores for combined cognition and individual cognitive tests. I used age, in years divided by 10, as the timescale centred at age 56 years, the mean age at phase 5. This means that coefficients from analyses of cognitive change are henceforth presented as number of standard deviations change per 10 years increasing age.

I then used likelihood ratio test to examine for evidence against the null hypothesis that a model with random intercept and slope did not give better fit than a more parsimonious model fitted with fixed intercept and random slope. There was very strong evidence to reject the null hypothesis ($p < 0.001$) meaning that all models were subsequently fitted with random intercept and random slope, allowing participants' cognition to vary at baseline and in subsequent trajectory. I then tested whether cognitive change was linear or whether there was evidence suggesting other patterns of change. I included a quadratic term in the model and used likelihood ratio test to examine whether this improved model fit, finding very strong evidence that it did so ($p < 0.001$) so all subsequent models treated cognitive change as non-linear.

I then undertook analyses of the association of low, medium, and high mean social contact during phase 1 to 5 and cognitive change from phase 5 to 12, with results presented adjusted for age and sex; and then additionally for all covariates described above (ethnicity, education, socioeconomic status, health behaviours, employment, and marital status). Covariates were used as recorded at phase 5.

As previous studies have suggested differences in the associations of lifestyle factors and cognitive trajectories between people who did and did not subsequently develop dementia, I then repeated my analyses, stratified for dementia status.

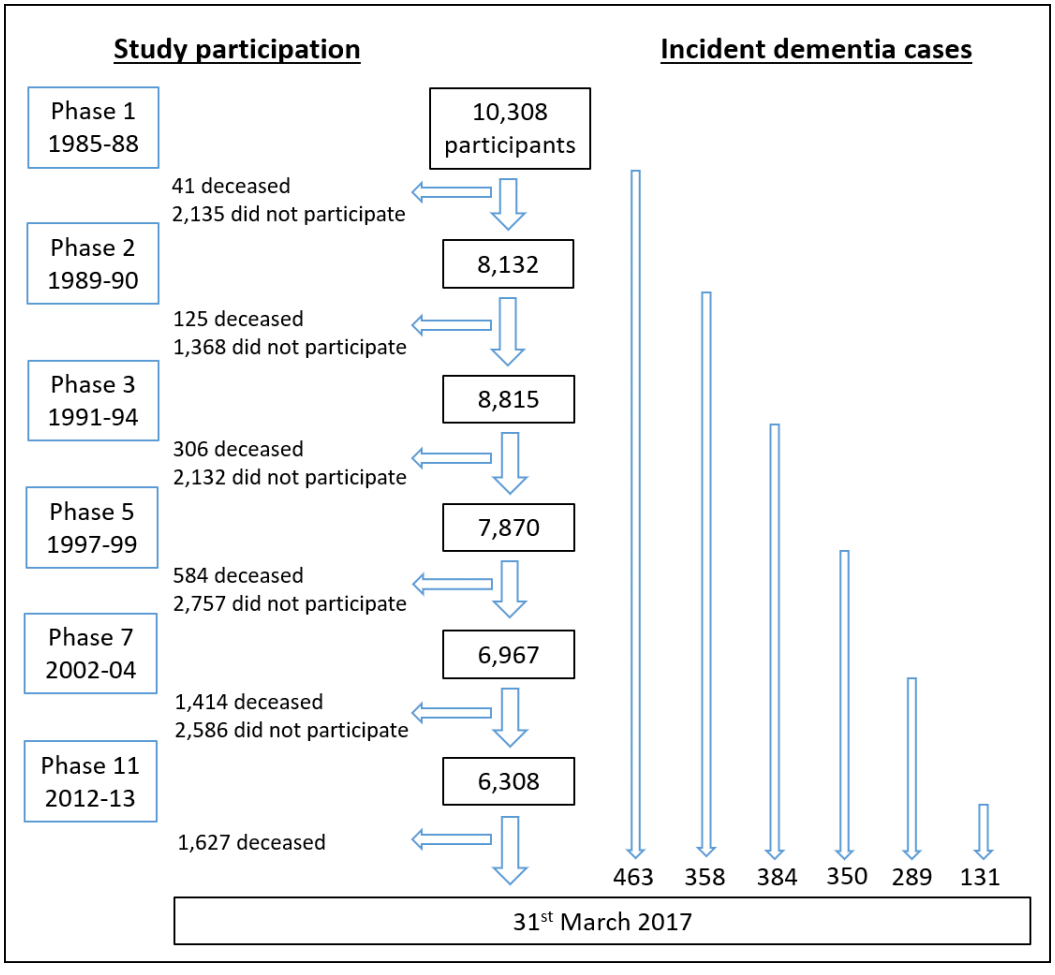
I used STATA SE version 14 for all my analyses and 2-sided p-values < 0.05 were considered statistically significant.

6.3 Results

6.3.1 Participation

Participation in the study phases during which social contact was measured and attrition by death and non-participation is described in a flow-chart (Figure 6-3), which also details the number of incident dementia cases following these study phases. 10,308 people initially participated in the study of whom 10,228 provided social contact data at some point during study follow-up. Of the full sample, 1,627 participants have died, and 463 cases of dementia have been ascertained through the linked electronic health records, before 31st March 2017. The mean duration of follow-up was 28.6 years (standard deviation (SD) = 4.9, maximum 31.8 years) and mean age at dementia diagnosis was 75.9 years (SD 5.6, min 56.9, max 86.0).

Figure 6-3: Flow chart of participation in Whitehall II study phases, and attrition, mortality and incident dementia cases.



Demographic characteristics of the sample are described in Table 6-1, and characteristics according to dementia status and baseline social contact are in Table 6-1 and Table 6-2; I will describe these associations in detail in section 6.3.5.

Around two thirds of study participants were male, with mean age 44.9 years and nearly three quarters were married at baseline assessment. Eighty nine percent of study participants were from white ethnic groups, and the remaining participants were South Asian (6%), African-Caribbean (3%) and from other ethnic groups (2%). There was a spread of socioeconomic class by employment grade from non-skilled positions to managerial and professional grades. Around one quarter had university education, one quarter had higher secondary (A-level) education and half had O-level or lower education. Just under one quarter were drinking more than 14 units alcohol per week, 18% were current smokers and median duration of moderate or vigorous exercise per week was 3 hours.

Table 6-1: Baseline demographics of study participants according to dementia status

Characteristic		All participants n=10,308		No dementia n=9,845		Dementia n=463		p value [a]
		n	%	n	%	n	%	
Sex	Male	6,895	66.9	6,635	67.4	260	56.2	
	Female	3,413	33.1	3,210	32.6	203	43.8	p<0.001
	Missing	0		0		0		
Age	Mean (SD)	44.9 (6.1)		44.7 (6.0)		50.2 (4.7)		
	Min, max	34.1, 56.3		34.1, 56.3		35.2, 56.0		p<0.001
	Missing	0		0		0		
Marital status	Married	7,608	73.8	7,285	74.0	323	69.8	
	Single	1,690	16.4	1,613	16.4	77	16.6	
	Divorced	833	8.1	782	7.9	51	11.0	p<0.001
	Widowed	139	1.4	129	1.3	10	2.2	
	Missing	38	0.4	36	0.4	2	0.4	
Ethnicity	White	9,181	89.1	8,787	89.3	394	85.1	
	Other	1,127	10.9	1,058	10.8	69	14.9	p=0.005
	Missing	0		0		0		
Social class	Professional	1,133	11.0	1,086	11.0	47	10.2	
	Managerial	1,895	18.4	1,828	18.6	67	14.5	
	Skilled non-manual	1,426	13.8	1,379	14.0	47	10.2	
	Skilled manual	1,976	19.2	1,920	19.5	56	12.1	p<0.001
	Partly skilled	1,541	15.0	1,473	15.0	68	14.7	
	Non-skilled	2,337	22.7	2,159	21.9	178	38.4	
	Missing	0		0		0		
Age leaving education	No qualifications	1,029	10.0	953	9.7	76	16.4	
	Lower secondary	3,870	37.5	3,666	37.2	204	44.1	
	Higher secondary	2,745	26.6	2,653	27.0	92	19.9	p<0.001
	Graduate	2,097	20.3	2,030	20.6	67	14.5	
	Postgraduate	567	5.5	543	5.5	24	5.2	
	Missing	0		0		0		
Alcohol (units/wk)	0	1,873	18.2	1,745	17.7	128	27.7	
	1-7	3,882	37.7	3,695	37.5	187	40.4	
	8-14	2,040	19.8	1,983	20.1	57	12.3	p<0.001
	>14	2,419	23.5	2,334	23.7	85	18.4	
	Missing	94	0.9	88	0.9	6	1.3	
Smoking	Never smoked	5,069	49.2	4,844	49.2	225	48.6	
	Ex-smoker	3,281	31.8	3,147	32.0	134	28.9	p<0.001
	Current smoker	1,886	18.3	1,787	18.2	99	21.4	
	Missing	72	0.7	67	0.7	5	1.1	
Physical activity (hrs/wk)	Med (IQR)	3 (1, 5)		3 (1,5)		2 (0, 5)		
	Min, max	0, 70		0, 70		0,25		p<0.001
	Missing	158		145		13		
All social contact score	Mean (SD)	7.0 (2.8)		7.0 (2.8)		6.7 (2.8)		
	Min, max	0, 16		0, 16		0, 14		p=0.02
	Missing	494		465		29		

Key: IQR = interquartile range; SD = standard deviation

Notes: [a] p value from student t-test for continuous variables and chi-squared test for categorical variables

Table 6-2: Baseline demographics of study participants according to baseline social contact

Characteristic		All participants n=10,308		Mean social contact score (SD)	p value [a]
	n	n	%		
Sex	Male	6,895	66.9	6.9 (2.7)	p<0.001
	Female	3,413	33.1	7.2 (2.8)	
	Missing	0		N/A	
Age	Mean (SD)	44.9 (6.1)		*r* = -0.02	p=0.08
	Min, max	34.1, 56.3			
	Missing	0		N/A	
Marital status	Married	7,608	73.8	7.0 (2.7)	p=0.06
	Single	1,690	16.4	6.8 (2.8)	
	Divorced	833	8.1	6.9 (2.9)	
	Widowed	139	1.4	6.9 (2.6)	
	Missing	38	0.4	6.5 (3.2)	
Ethnicity	White	9,181	89.1	7.0 (2.7)	p=0.57
	Other	1,127	10.9	6.9 (2.9)	
	Missing	0		N/A	
Social class	Professional	1,133	11.0	7.2 (2.5)	p=0.003
	Managerial	1,895	18.4	7.0 (2.6)	
	Skilled non-manual	1,426	13.8	6.9 (2.7)	
	Skilled manual	1,976	19.2	6.9 (2.7)	
	Partly skilled	1,541	15.0	6.8 (2.8)	
	Non-skilled	2,337	22.7	7.0 (3.0)	
	Missing	0		N/A	
Age leaving education	No qualifications	1,029	10.0	7.1 (2.9)	p=0.39
	Lower secondary	3,870	37.5	7.0 (2.9)	
	Higher secondary	2,745	26.6	6.9 (2.7)	
	Graduate	2,097	20.3	7.0 (2.6)	
	Postgraduate	567	5.5	6.8 (2.5)	
	Missing	0		N/A	
Alcohol (units/wk)	0	1,873	18.2	6.6 (3.1)	p<0.001
	1-7	3,882	37.7	7.0 (2.7)	
	8-14	2,040	19.8	7.1 (2.6)	
	>14	2,419	23.5	7.1 (2.7)	
	Missing	94	0.9	7.0 (2.5)	
Smoking	Never smoked	5,069	49.2	6.9 (2.7)	p=0.06
	Ex-smoker	3,281	31.8	7.0 (2.7)	
	Current smoker	1,886	18.3	7.1 (2.8)	
	Missing	72	0.7	7.3 (2.6)	
Physical activity (hrs/wk)	Med (IQR)	3 (1, 5)		*r* = 0.11	p<0.001
	Min, max	0, 70			
	Missing	158			

Key: IQR = interquartile range; SD = standard deviation

Notes: [a] p value from student t-test for continuous variables and chi-squared test for categorical variables

6.3.2 Social contact

Mean social contact as a combination of contact frequency with friends and relatives, and for contact with friends and relatives separately, at age 50, 60 and 70 years is summarised in Table 6-3. Social network contact increased from age 50 to 60 to 70 years (total social network score 6.9, 7.5, 8.1 respectively) with most of this change driven by increasing contact with friends and acquaintances (from 3.9 at 50 years to 4.7 at 70 years) and, to a lesser extent, by contact with relatives (which increased from 3.0 to 3.4). A full range of scores on the scales were used by participants at each age-point and these scores were normally distributed (skewness -0.09, -0.07, -0.19 and kurtosis 2.59, 2.62, 2.65 for all social contact at age 50, 60, and 70 years respectively).

Table 6-3: Description of social contact and contact change at age points

Age (n)		Social contact scale		Friend subscale		Relative subscale	
		n	%	n	%	n	%
50 years (8,853)	Mean (SD)	6.9 (2.8)		3.9 (1.9)		3.0 (1.8)	
	Range	0, 16		0, 8		0, 8	
	Missing	166	1.9	0	0	160	1.8
60 years (7,710)	Mean (SD)	7.5 (3.0)		4.3 (2.0)		3.2 (1.9)	
	Range	0, 16		0, 8		0, 8	
	Missing	183	2.4	0	0	173	2.2
70 years (5,137)	Mean (SD)	8.1 (3.1)		4.7 (2.0)		3.4 (2.0)	
	Range	0, 16		0, 8		0, 8	
	Missing	153	3.0	0	0	152	3.0
Change from 60 years to 70 years	n	4,591		4,809		4,664	
	Mean (SD)	+0.5 (2.8)		+0.4 (1.9)		+0.1 (1.9)	
	Range	-9, 11		-7, 8		-7, 8	
	Remain high	805	17.5	893	18.6	807	17.3
	Remain medium	731	15.9	812	16.9	760	16.3
	Remain low	859	18.7	780	16.2	947	20.3
	Increasing	1,341	29.2	1,486	30.9	1,110	23.8
	Decreasing	855	18.6	838	17.4	1,040	22.3

Notes: Remain high = high at 60 years and 70 years; Remain medium = medium at 60 years and 70 years; Remain low = low at 60 years and 70 years; Increasing = change from low at 60 years to medium or high at 70 years or from medium at 60 years to high at 70 years; Decreasing = change from high at 60 years to medium or low at 70 years or from medium at 60 years to low at 70 years.

Mean change in social contact between 60 and 70 years in the 4,591 participants who gave data at each of these age points was an increase of 0.5 points (Table 6-3); most of this increase was explained by increasing contact with friends (0.4 points). Social change was normally distributed, with a range from decrease by 9 points to increase by 11 points. There was weak positive correlation between social contact with friends and relatives at each age point (r = 0.15 at 50 years, 0.17 at 60 years, 0.17 at 70 years). Correlation between social contact measures at successive study phases was moderate. For contact with friends at 50 and 60 years, r = 0.51; and at 60 and 70 years, r = 0.51. For contact with relatives at 50 and 60 years, r = 0.48; and at 60 and 70 years r = 0.52.

6.3.3 Cognitive function

Cognitive function at successive study phases is summarised in Table 6-4. Mean scores on all tests declined over successive study phases: at phase 5, mean score on Alice Heim test of reasoning was 46.4/65 at phase 5 and 42.9 at phase 12. Verbal memory scores declined from 6.9/20 to 5.3 /20 and number of animals and s-words fell from 16.4 and 16.8 to 15.0 and 14.9 respectively. In these data, there was no evidence of a practice effect whereby scores improved with repeated testing.

Table 6-4: Description of cognitive function test scores at each study phase

Study phase (n)		Reasoning (0-65)	Verbal memory (0-20)	Verbal fluency (animals)	Verbal fluency (s-words)
5 (7,870)	Mean (SD)	46.4 (11.3)	6.9 (2.4)	16.4 (4.2)	16.8 (4.4)
	Range	1, 65	0, 18	1, 35	1, 35
	Missing	1,841 23.4	1,875 23.8	1,856 23.6	1,863 23.7
7 (6,967)	Mean (SD)	43.6 (11.3)	6.8 (2.4)	15.6 (3.9)	15.7 (4.2)
	Range	1, 65	1, 17	1, 33	1, 35
	Missing	605 8.7	638 9.2	620 8.9	635 9.1
9 (6,761)	Mean (SD)	43.3 (11.3)	6.2 (2.2)	15.2 (3.8)	15.3 (4.0)
	Range	2, 65	1, 16	1, 35	1, 35
	Missing	690 10.2	721 10.7	705 10.4	713 10.6
11 (6,308)	Mean (SD)	43.3 (11.4)	6.0 (2.4)	14.9 (4.0)	15.2 (4.2)
	Range	0, 65	0, 20	0, 29	0, 35
	Missing	792 12.6	819 13.0	792 12.6	795 12.6
12 (5,632)	Mean (SD)	42.9 (11.2)	5.3 (2.2)	15.0 (3.9)	14.9 (4.6)
	Range	0, 64	0, 18	0, 35	0, 35
	Missing	855 15.2	885 15.7	868 15.4	868 15.4

Correlation between the three different cognitive tests was variable. There was moderate/strong correlation between scores on verbal fluency and reasoning tests (between 0.60 and 0.64 at the five study phases), but there was weaker correlation between test scores on verbal fluency and verbal memory tests (0.37 to 0.43) and between tests of verbal memory and reasoning (0.33 to 0.42). There was strong correlation, however, between performance on combined cognitive function measured at successive study phases as shown in Table 6-5.

Table 6-5: Correlation between scores on standardised combined cognitive test in each study phase

	Phase 5	Phase 7	Phase 9	Phase 11	Phase 12
Phase 5	1				
Phase 7	0.84	1			
Phase 9	0.81	0.85	1		
Phase 11	0.79	0.81	0.84	1	
Phase 12	0.74	0.78	0.82	0.83	1

Notes: Correlation coefficients derived from Pearson correlation test; $p < 0.001$ for all coefficients.

6.3.4 Attrition and missingness bias

Non-participation in the study at each age point was more likely in people who were younger, female, unmarried and with lower baseline social contact, but it was not associated with dementia incidence (Appendix 9). Missing social contact data in those who participated at each age point was not associated with age or sex but more likely in unmarried people, those with lower level of baseline social contact and in those who later developed dementia (Appendix 10). This justifies my use of inverse probability weighting to weight results according to participation in adjusted models, thereby reducing the effect of attrition and missing data.

Missing cognitive function data in people participating at successive study phases was more likely in older, female, and unmarried people, those with lower social contact

and those who went on to develop dementia (Appendix 11). The mixed linear models I used to examine cognitive change includes participants with any social contact data, but the association of missing data with lower social contact and higher risk of dementia may mean that association between social contact and cognitive decline is underestimated.

6.3.5 Covariates

In univariate analyses, dementia status was associated with female sex, age, marital status, ethnicity, education, alcohol consumption, smoking, physical activity and social contact at baseline (Table 6-1). Baseline social contact (Table 6-2) was associated with female sex, socioeconomic class, alcohol consumption, and physical activity.

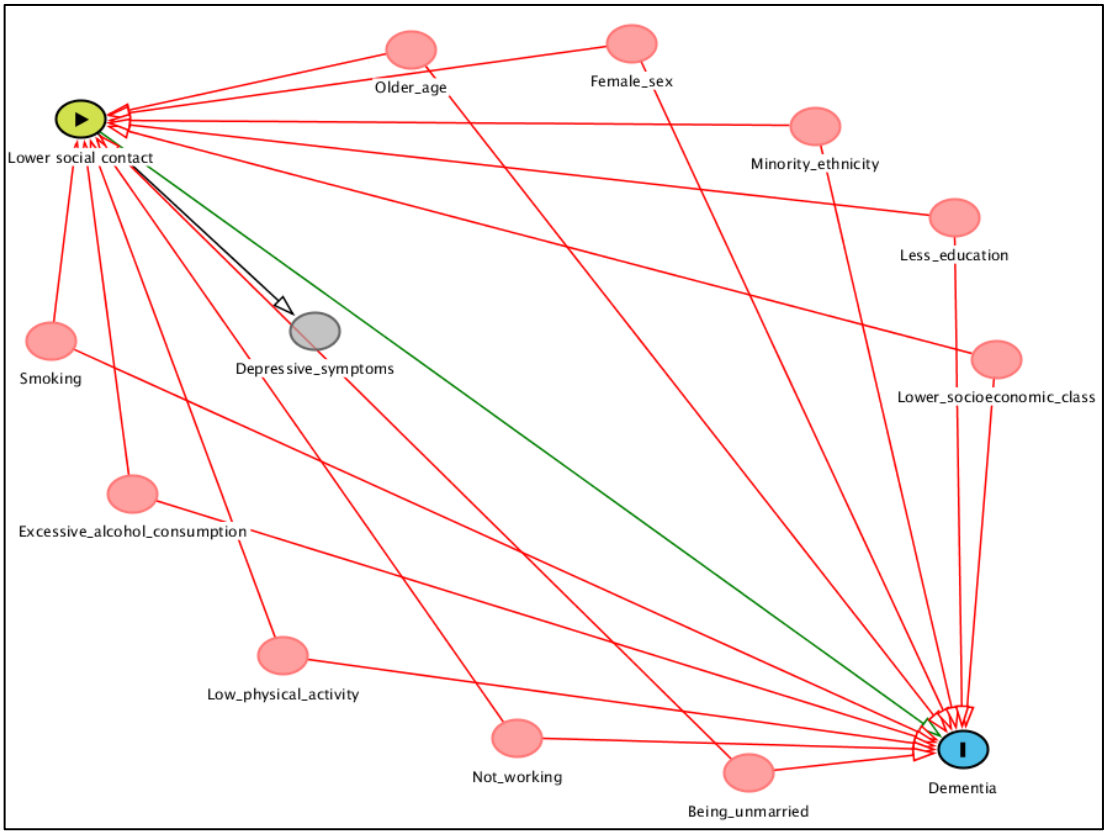
Level of depressive symptoms was associated with baseline social contact but not dementia status in univariate analyses. Furthermore, a previous analysis of the association between midlife depressive symptoms and dementia incidence using the Whitehall II cohort (Singh-Manoux et al., 2017) indicated that depressive symptoms were not associated with dementia risk, so I chose not to adjust my analyses for depressive symptoms.

Social contact was associated with whether participants were continuing to work (compared to unemployed or retired) at age 60 and 70 years and employment at 60 and 70 years was also strongly associated with subsequent dementia status. Previous studies have suggested that retirement may be associated with adverse cognitive trajectories (Roberts et al., 2011, Meng et al., 2017, Xue et al., 2018), supporting the need to adjust for whether participants are in employment.

I drew a directed acyclic graph to demonstrate associations between potential covariates and social contact and dementia (Figure 6-4). Although marital status was marginally not associated with social contact, I ran models with marital status as a covariate, as the social contact measurement used in Whitehall II asked about contact with relatives outside the home, and so did not take account of social contact with a

spouse or cohabiting partner, which is usually daily. Furthermore I previously (chapter 4) found that being married, without adjustment for social contact, is associated with lower dementia risk (Sommerlad et al., 2018b) and I wanted in this study to examine the effect of social contact frequency independent of marital status.

Figure 6-4: Directed acyclic graph showing relationships between lower social contact, dementia and potential covariates



6.3.6 Association between social network contact at 50, 60, and 70 years and incident dementia

In adjusted and weighted models, higher amount of social contact was associated with reduced risk of dementia at age 60 years (hazard ratio (HR) for one standard deviation increase in social contact = 0.88, 95% CI 0.79, 0.98) (Table 6-6). Point estimates of the association of social contact at age 50 years and 70 years and dementia were similar (HR 0.92 (0.83, 1.02) and 0.91 (0.78, 1.06) respectively) but associations were not statistically significant. Higher contact with friends at age 60 years was associated with lower risk of dementia (HR = 0.90 (0.81, 1.00)) but

associations were not found for contact with friends at other age points. Social contact with relatives at age 50, 60, or 70 years was not associated with dementia.

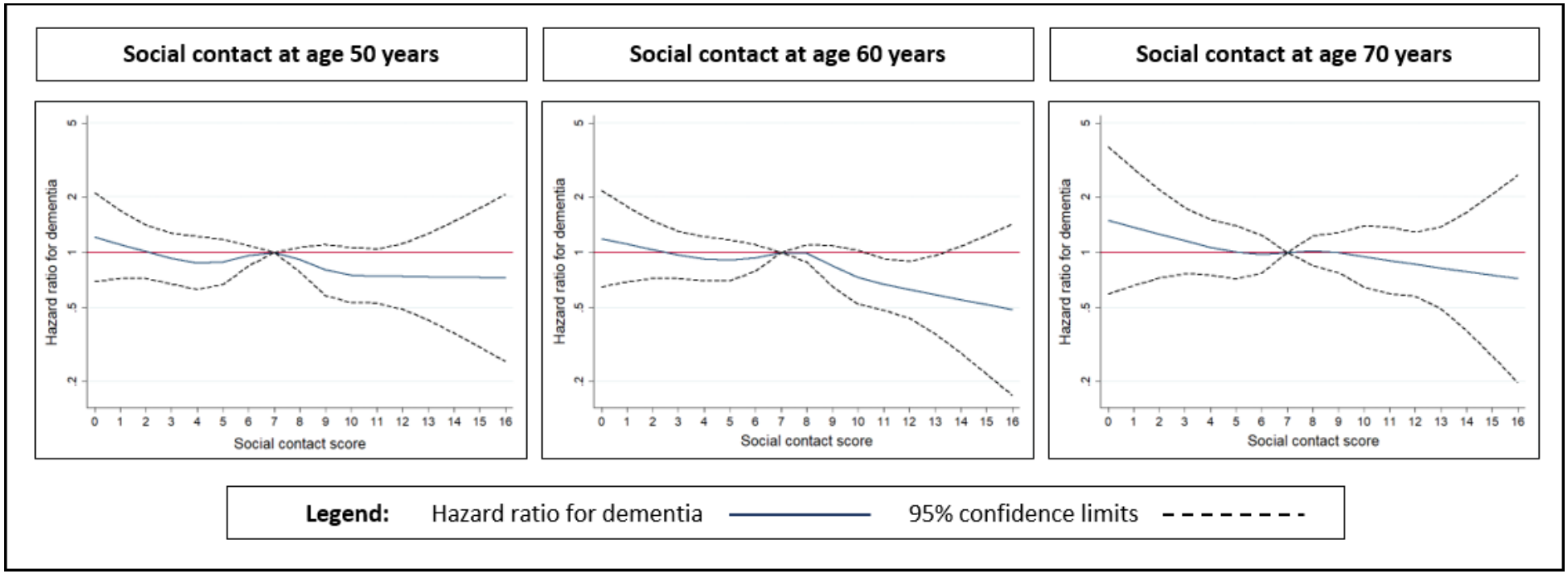
I plotted the hazard ratios for dementia associated with each social contact score at age 50, 60, and 70 years with the mean score, 7, as reference value (Figure 6-5). The association was linear, which was confirmed with examination of a LOWESS plot.

Table 6-6: **Association between social network contact at different ages and subsequent incident dementia: hazard ratio for dementia associated with higher levels of social network contact**

Age			**50 years**	**60 years**	**70 years**
Mean years f/u			**23.1 (6.2)**	**14.6 (6.9)**	**7.5 (4.4)**
Number included in fully adjusted model (weighted n)			**8,487 (10, 278)**	**7,439 (10,141)**	**4,888 (9,237)**
Number of incident dementia cases in those who participated			**362**	**351**	**221**
All social contact	**Adjusted for age and sex**	Per standard deviation increase in social contact	0.90 (0.81, 1.00)	**0.86 (0.77, 0.95)**	0.87 (0.75, 1.01)
	+ education, social class, ethnicity		0.91 (0.82, 1.01)	**0.88 (0.79, 0.98)**	0.89 (0.77, 1.04)
	+ smoking, alcohol and exercise		0.92 (0.83, 1.02)	**0.88 (0.79, 0.98)**	0.91 (0.78, 1.06)
	+ employment status		0.92 (0.83, 1.02)	**0.88 (0.79, 0.98)**	0.91 (0.78, 1.06)
	+ marital status		0.92 (0.83, 1.02)	**0.88 (0.79, 0.98)**	0.91 (0.78, 1.06)
n included in fully adjusted model (weighted n)			**8,643 (10,279)**	**7,617 (10,141)**	**5,035 (9,236)**
Friend contact	**Adjusted for age and sex**	Per standard deviation increase in social contact	0.92 (0.83, 1.03)	**0.86 (0.78, 0.96)**	**0.86 (0.76, 0.99)**
	+ education, social class, ethnicity		0.95 (0.85, 1.05)	**0.90 (0.80, 1.00)**	0.89 (0.77, 1.02)
	+ smoking, alcohol and exercise		0.96 (0.86, 1.07)	**0.90 (0.81, 1.00)**	0.91 (0.79, 1.05)
	+ employment status		0.96 (0.86, 1.07)	0.90 (0.81, 1.00)	0.92 (0.80, 1.05)
	+ marital status		0.96 (0.86, 1.07)	**0.90 (0.81, 1.00)**	0.91 (0.80, 1.05)
n included in fully adjusted model (weighted n)			**8,493 (10,278)**	**7,449 (10,141)**	**4,889 (9,240)**
Relative contact	**Adjusted for age and sex**	Per standard deviation increase in social contact	0.91 (0.81, 1.01)	0.92 (0.83, 1.03)	0.93 (0.80, 1.08)
	+ education, social class, ethnicity		0.90 (0.81, 1.00)	0.92 (0.83, 1.03)	0.94 (0.80, 1.09)
	+ smoking, alcohol and exercise		0.91 (0.82, 1.01)	0.92 (0.83, 1.03)	0.94 (0.80, 1.10)
	+ employment status		0.91 (0.82, 1.01)	0.92 (0.83, 1.03)	0.94 (0.81, 1.11)
	+ marital status		0.91 (0.82, 1.02)	0.92 (0.83, 1.03)	0.94 (0.80, 1.11)

Notes: Weighted according to inverse of probability of inclusion in fully adjusted model; Bold results indicate $p<0.05$.

Figure 6-5: Association of frequency of social contact with friends and relatives at age 50, 60 and 70 years and incident dementia: plot of hazard ratio for dementia according to social contact score



Notes: Cox regression models adjusted for age, sex, education, social class, ethnicity, smoking, alcohol, exercise, employment status and marital status. Reference for social contact is score 7 (mean score at baseline)

In the sensitivity analysis without inverse probability weighting, results were similar at age 50 and 60 years (Appendix 12). The association between social contact and dementia was slightly underestimated at age 70 years (unweighted = 0.95 (0.83, 1.09 v weighted 0.91 (0.78, 1.06)). Fully adjusted and weighted results using data which did not include the imputed phase 1 friend responses were also similar to primary results (Appendix 13).

6.3.7 Association between change in social network contact and incident dementia

There was no association between change in social network score from age 60 to 70 years and incident dementia (Table 6-7), with mean follow-up from age 70 years of 7.6 years. One point increase in all social contact from 60 to 70 years was associated with HR for dementia 1.00 (0.94, 1.06). Compared to participants whose social contact remained high, no other category of social change was associated with significantly higher risk of dementia.

Table 6-7: Association between social contact change from age 60 to 70 years and subsequent incident dementia during mean 7.5 years follow-up: hazard ratio for dementia associated with continuous and categorical social contact change

		All social contact	Friend contact	Relative contact
n included in fully adjusted model (weighted n)		**4,534 (8,398)**	**4,534 (8,132)**	**4,534 (8,401)**
Adjusted for age, sex and baseline social contact	*Per one-point increase in social contact score from age 60 to 70*	0.99 (0.93, 1.05)	0.97 (0.89, 1.05)	1.00 (0.93, 1.09)
+ education, social class, ethnicity		1.02 (0.94, 1.05)	0.98 (0.90, 1.06)	1.01 (0.93, 1.09)
+ smoking, alcohol and exercise		1.00 (0.94, 1.06)	0.99 (0.91, 1.07)	1.01 (0.93, 1.10)
+ employment status		1.00 (0.94, 1.06)	0.99 (0.91, 1.07)	1.01 (0.93, 1.10)
+ marital status		1.00 (0.94, 1.06)	0.99 (0.91, 1.07)	1.01 (0.93, 1.10)
Fully adjusted *Categorical*	Remain high (ref)	1	1	1
	Remain medium	1.33 (0.81, 2.19)	1.12 (0.64, 1.96)	0.77 (0.44, 1.37)
	Remain low	1.18 (0.70, 1.99)	1.22 (0.71, 2.11)	1.12 (0.68, 1.85)
	Increasing	1.28 (0.81, 2.02)	1.38 (0.86, 2.20)	1.08 (0.70, 1.67)
	Decreasing	1.07 (0.63, 1.82)	1.15 (0.66, 2.00)	0.91 (0.58, 1.44)

Notes: All results weighted according to inverse of probability of inclusion in fully adjusted model. Remain high = high at 60 years and 70 years; remain medium = medium at 60 years and 70 years; remain low = low at 60 years and 70 years; increasing = change from low at 60 years to medium or high at 70 years or from medium at 60 years to high at 70 years; decreasing change from high at 60 years to medium or low at 70 years or from medium at 60 years to low at 70 years

6.3.8 Association between social network contact and subsequent cognitive decline

Cognitive function was measured in 7,540 participants and the mean number of cognitive assessments of these study participants was 3.8. Mean time from first to last cognitive assessment was 14.3 (SD 5.6, max 19.4) years. In longitudinal analyses, the mean decline in combined cognitive z-score in the cohort was 0.40 (0.40, 0.41) standard deviations per 10 years. Decline per 10 years for individual tests was 0.33 (0.32, 0.35) standard deviations for verbal fluency; 0.41 (0.39, 0.42) standard deviations for verbal memory; 0.25 (0.24, 0.25) standard deviations for reasoning.

In adjusted mixed linear models examining the association of social contact frequency and cognition (Table 6-8), I found that higher mean total social contact during 10 years from phase 1 to 5 was associated with higher baseline cognition; high v low social contact tertile had 0.07 (0.03, 0.11) standard deviations higher combined cognitive score. Baseline performance on tests of verbal fluency (0.08 (0.03, 0.12) standard deviations) and verbal memory (0.05 (0.00, 0.10) standard deviations) was higher for participants with more frequent preceding social contact, but baseline reasoning was not association with social contact. These associations of social contact and baseline cognition were consistent for contact with friends, but not contact with relatives where I found no baseline cognitive differences.

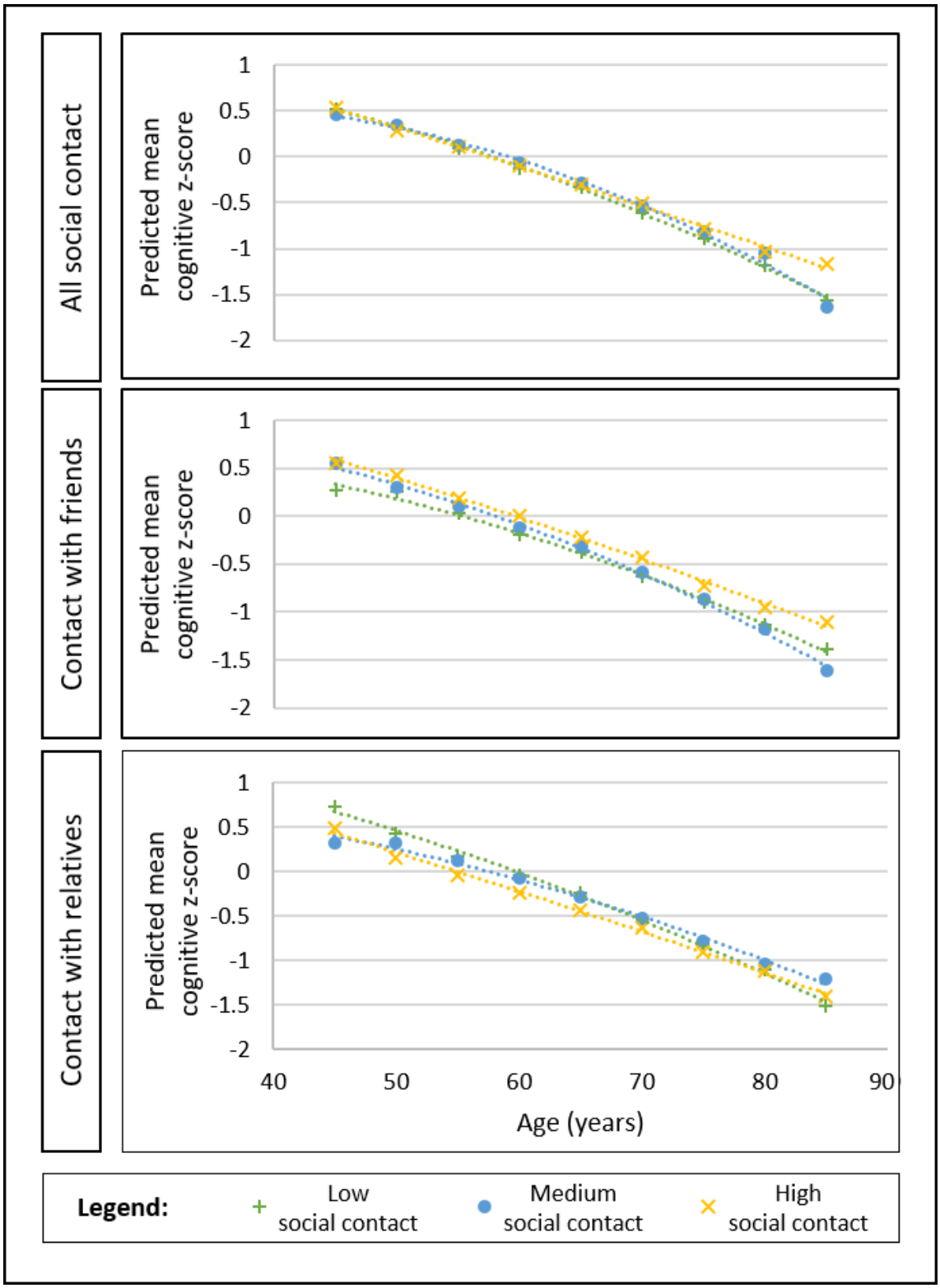
Higher mean total social contact during 10 years between phase 1 and 5 was not associated with rate of cognitive decline (cognitive change per 10 years in high v low social contact = -0.01 (-0.03, 0.01) standard deviations). There was evidence only from analysis of contact frequency with friends and combined cognitive trajectory of association; those with high contact with friends had 0.03 (0.00, 0.05, p = 0.02) standard deviations greater cognitive decline over 10 years than those with low contact. There was no association between social contact with relatives and cognitive decline. A plot of trajectories of cognitive decline according to tertiles of preceding mean social contact with friends and relatives are shown in Figure 6-6. Full results from the adjusted models for the low, medium and high tertiles are in Appendix 15 and show a gradient in cognition across the three tertiles of social contact.

Table 6-8: Differences in baseline cognition and cognitive change per 10 years between Whitehall II participants with preceding high and low social contact frequency

Social domain	Cognitive domain	Age and sex-adjusted differences		Fully-adjusted differences	
		Baseline cognition (standard deviations)	**Cognitive change** (standard deviations / 10y)	**Baseline cognition** (standard deviations)	**Cognitive change** (standard deviations / 10y)
All social contact	Combined cognition	**0.09 (0.04, 0.14)**	-0.00 (-0.03, 0.02)	**0.07 (0.03, 0.11)**	-0.01 (-0.03, 0.01)
	Verbal fluency	**0.10 (0.05, 0.15)**	0.00 (-0.02, 0.03)	**0.08 (0.03, 0.12)**	-0.00 (-0.03, 0.02)
	Verbal memory	**0.05 (0.00, 0.10)**	0.00 (-0.03, 0.03)	**0.05 (0.00, 0.10)**	-0.01 (-0.04, 0.02)
	Reasoning	0.03 (-0.03, 0.08)	-0.00 (-0.02, 0.02)	0.01 (-0.03, 0.05)	-0.01 (-0.03, 0.01)
Friend contact	Combined cognition	**0.22 (0.17, 0.28)**	-0.02 (-0.05, 0.00)	**0.08 (0.03, 0.12)**	**-0.03 (-0.05, -0.00)**
	Verbal fluency	**0.22 (0.17, 0.27)**	-0.02 (-0.05, 0.01)	**0.10 (0.05, 0.15)**	-0.02 (-0.05, 0.00)
	Verbal memory	**0.10 (0.05, 0.15)**	-0.02 (-0.05, 0.02)	**0.04 (0.01, 0.09)**	-0.02 (-0.06, 0.01)
	Reasoning	**0.17 (0.12, 0.22)**	-0.00 (-0.03, 0.02)	0.02 (-0.02, 0.06)	-0.01 (-0.03, 0.01)
Relative contact	Combined cognition	**-0.13 (-0.19, -0.07)**	0.01 (-0.02, 0.03)	0.01 (-0.03, 0.06)	0.00 (-0.02, 0.03)
	Verbal fluency	**-0.10 (-0.16, -0.04)**	0.01 (-0.02, 0.04)	0.02 (-0.03, 0.07)	0.00 (-0.03, 0.03)
	Verbal memory	**-0.08 (-0.14, -0.03)**	0.03 (-0.01, 0.06)	-0.01 (-0.06, 0.05)	0.02 (-0.02, 0.05)
	Reasoning	**-0.17 (-0.23, -0.11)**	0.00 (-0.02, 0.02)	0.00 (-0.04, 0.05)	-0.00 (-0.03, 0.02)

Notes: Baseline cognition centred at age 56 years; Number included in analysis for combined cognition = 7,092, for verbal fluency and verbal memory = 7,120, for reasoning = 7,132; Fully adjusted model adjusted for age, sex, education, social class, ethnicity, smoking, alcohol, exercise, employment status, and marital status at baseline; Bold figures indicate $p < 0.05$

Figure 6-6: Trajectories of cognitive change according to level of preceding frequency of social contact



Notes: Social contact is mean of responses at study phases 1, 2, 3, and 5 and divided into tertiles of approximately equal size; Cognitive function is combined verbal fluency, verbal memory and reasoning from study phase 5, 7, 9, 11 and 12, standardised to z-score with mean = 0 and standard deviation = 1

I repeated my analyses stratified for subsequent dementia status. Mean cognitive decline in the 7,253 people who did not subsequently develop dementia was 0.39 (0.38, 0.40) standard deviations per 10 years while decline in the 298 people who had been cognitively assessed and subsequently did develop dementia was 0.95 (0.88, 1.03) standard deviations per 10 years.

Differences in baseline cognition between those with higher preceding frequency of social contact were more pronounced in those who subsequently went on to develop dementia than in those who did not (dementia cases: combined baseline cognition score was 0.42 (0.06, 0.75) standard deviations higher for those with high social contact compared to low; dementia free 0.06 (0.02, 0.10). The higher rate of cognitive decline in those with more frequent social contact with friends was also of greater magnitude in those who went on to develop dementia than those who did not. Combined cognitive decline per 10 years was 0.28 (0.06, 0.50) standard deviations greater in those with high v low preceding social contact for people who went on to develop dementia and 0.03 (0.00, 0.05) for those who did not.

6.4 Discussion

6.4.1 Main findings

In this large prospective study with over 28 years of follow-up, I examined the association of frequency of social contact with risk of dementia and cognitive decline, aiming to address the following objectives:

1. *Test the association between frequency of social contact with friends and relatives at 50, 60, and 70 years of age and incident dementia*

I found evidence that more frequent social network contact at age 60 years was associated with 12% reduced risk of subsequent dementia. However, while there was a similar hazard ratio point estimate, there was no evidence of an association between social contact at age 50 or 70 years and dementia risk. The association at 60 years was driven by social contact with friends, rather than relatives.

2. *Examine association between change in social contact and incident dementia*

Changes in frequency of social contact from age 60 to 70 years, with mean 7.6 years subsequent follow-up, were not associated with dementia incidence.

3. *Examine the association between social contact and subsequent cognitive decline*

I found that more frequent social contact over 10 years from mean age 45 to 55 was associated with higher level of baseline cognition but not with rate of subsequent cognitive change; this association was related to social contact with friends.

These findings taken together provide some evidence that having more frequent social contact during late-middle-age reduces dementia risk, independent of other social and lifestyle factors. However, the borderline statistical significance and inconsistent associations found in my study weaken confidence in these findings.

In this discussion, I will first explore the evidence from my study and previous research which supports the argument that social contact causes better cognition and reduced dementia risk. I will then consider other potential explanations for these findings: chance, selection and attrition bias, measurement bias, confounding, or reverse causation. I will discuss the strengths and limitations of my study in these contexts. I will then compare my results with those from other studies and discuss overall conclusions and clinical and research implications of this study.

6.4.2 Evidence that social contact improves cognition and reduces dementia

This association between social contact frequency and dementia and cognition which I found in my study may be related to social contact directly improving cognition and reducing dementia risk. This association meets a number of Hill's criteria for causation (Hill, 1965) including consistency, temporality, biological gradient, and plausibility, which supports this argument.

6.4.2.1 Consistency

The association between social contact and subsequent incident dementia was similar in size at age 50, 60, and 70 years (HR = 0.92, 0.88, 0.91 respectively), although only statistically significant at age 60 years. The 95% confidence intervals for the estimates at these three age points overlapped and this was also the case for estimates of the association between contact with friends, and contact with relatives, and dementia incidence.

6.4.2.2 Temporality

Measurements of social contact preceded assessment for dementia (mean 15 years between assessment at age 60 years and end of follow-up) and this is beyond the time at which prodromal changes of dementia could feasibly lead to reverse causation bias, as discussed in section 6.1.1. My analysis of the association between social contact and cognitive change measured mean social contact over a period of 10 years prior to measurement of cognition and the method of analysis, using random intercept and slope took account of baseline cognitive differences. Although I did not find that cognitive decline was slower in people with more frequent social contact, I found that cognition at mean 55 years was higher in those with more frequent social contact between 45 and 55 years of age, and that this difference was maintained throughout follow-up. This is consistent with other studies examining known dementia risk factors, which I will discuss in more detail in section 6.4.9.2.

6.4.2.3 Biological gradient

The association between social contact frequency and dementia was linear, as described in section 6.3.6 and my findings shown in Figure 6-5 suggested a biological gradient whereby greater frequency of social contact was associated with lower dementia risk. The association between social contact and cognition also indicated 'dose-response' gradient between tertiles of social contact frequency as discussed in section 6.3.8 and shown in Appendix 15.

6.4.2.4 Plausibility

I discussed potential mechanisms by which social contact may act to reduce risk of dementia in section 2.3.1. It is plausible that having more social contact could build cognitive reserve by exercising cognitive domains such as memory, language, reasoning, and speed of information processing, thereby delaying dementia onset. Social contact could affect subsequent health behaviours, such that individuals who are socially active have healthier diets, drink less alcohol, smoke less and take more exercise, all of which are lifestyle factors with established links to dementia. Having more social contact could also reduce negative emotional states such as loneliness, depressed mood and thereby reduce the biological effect of stress on cognition and brain function.

My findings that contact with friends, but not relatives, was associated with subsequent dementia and cognitive function could indicate that greater cognitive effort is involved in keeping in contact with more distal social relations (friends) compared to relatives, which builds cognitive reserve. Alternatively, contact with friends could theoretically lead to greater enjoyment and lower stress (Adams and Blieszner, 1995) as friends, unlike family, can be selected. Health behaviours encouraged by friends and family may also differ. However, I could not find empirical literature examining these differences, so these hypotheses are speculative.

Another possible explanation for the difference between friend and relative contact is that the number of relatives is usually limited, whereas the number of potential friendships is theoretically unlimited. So those with high cognition and low risk of dementia may not have relatives but instead have many friends, which would strengthen the association for friends but not for relatives. The scale used in my study has a ceiling effect for relatives but not friends: someone who has only one available relative outside of their household but who has maximum frequency of contact with that relative (i.e. daily), could only score 5 out of 8 on the scale. This may therefore result in underestimation of the association between frequency of contact with relatives and cognition and dementia.

My analyses provide some evidence supporting the cognitive reserve hypothesis as an explanation for the finding of social contact being associated with dementia risk. Higher mean level of social contact during age 45 to 55 years was associated with higher baseline cognition, taking into account other potential causes of cognitive difference such as level of education and socioeconomic class, suggesting that social contact during early to mid-life may have contributed to building cognitive reserve. There was no association with cognitive decline over the subsequent 14.3 years, which is consistent with several studies of other markers of cognitive reserve. An alternative explanation, whereby higher level of cognition results in more frequent social contact, is possible and I will discuss the results from this analysis in the context of previous studies in more detail in section 6.4.9.2.

6.4.3 Measurement error and bias

There is potential for random error when measuring any domain and such error results in loss of power to detect association, but should not bias results in the direction of either under- or overestimation (Hutcheon et al., 2010). By contrast, measurement bias results from systematic error in measurement and leads to results incorrectly favouring a particular result (Millsap and Everson, 1993). I will discuss below potential sources of error and bias in measuring social contact and ascertaining dementia cases in the Whitehall II study.

6.4.3.1 Social contact

I discussed in section 2.2.2 the challenges of measuring social contact. Use of self-report leads to potential for measurement error as study participants may struggle to accurately quantify their frequency of social contact. Repeated measurement may have reduced the impact of this by allowing, in my analysis of the association with dementia incidence, examination of the effect at different times and, in my analysis of cognition, examination of mean social contact. Questionnaire-derived data also lacks detail as we have no information about the nature of the contact between study participants, such as conversational activity and how cognitively stimulating the social contact may have been. Although Whitehall II asked about quality of support from close personal contacts using the close person questionnaire (Stansfeld and

Marmot, 1992), this does not ask about the nature of contact with the broader social network, so detail on this is missing in my study. Furthermore, questions related to face-to-face contact and did not cover telephone, email, or other computer contact. Therefore detail on this is lost, potentially resulting in lower power to detect association. However, face-to-face contact is likely to be the most cognitively stimulating type of social contact, as it exercises more cognitive domains, so there is value in assessing this specifically.

Triangulation with informant reports would improve the accuracy of measurement of social contact, and therefore confidence in my findings. In addition, there is potential in future for technological approaches to measuring social contact in vivo, such as through analysing smartphone data on telephone call frequency or even potentially proximity to other social contacts. However, such approaches are in their infancy and would lack sufficiently long follow-up to be of use.

Measurement bias, whereby there are differences in the accuracy of exposure measurements in people with and without the outcome of interest, is less likely in a longitudinal cohort study where assessment of the exposure takes place before assessment of outcome. However, using self-reported social contact data could potentially introduce bias, as those who developed dementia soon after social assessment may lack insight into changes in their social function, resulting in overestimation of social contact at these times. However, the long follow-up in my analyses meant that I was unlikely to include measurements of social contact during dementia prodrome. Even if such measurements were included, I found in a previous study that people with mild dementia could rate their social function with moderate correlation with carer rating (Sommerlad et al., 2017), suggesting that this measurement bias may be limited.

There is therefore no compelling evidence for bias in the measurement of social contact frequency in my study, although random measurement error may have resulted in reduced precision in the estimates from my study.

6.4.3.2 Dementia ascertainment

The Whitehall II study's ascertainment of dementia status using electronic health records, rather than diagnosing dementia through standardised clinical examination of all study participants, is a potential source of measurement error and bias. The three data sources used are likely to include most diagnosed dementia, as I discussed in section 6.2.2.2.1, but national diagnosis rates are currently estimated to be only 68% (NHS Digital, 2018), so there is very likely to be underestimation of true dementia cases leading to loss of statistical power. Use of electronic health records however reduces the risk of attrition bias compared to deriving dementia cases by clinically examining all participants, as people who develop dementia may be less likely to attend study follow-up and therefore diagnosis may be missed.

I estimated the age-standardised prevalence of dementia in Whitehall II participants, based on their age in 5 year bands at the end of follow-up (31st March 2017 or death), and using data from the Cognitive Function and Aging II study (Matthews et al., 2013). I found that 523 dementia cases would be expected amongst Whitehall participants (full results in Appendix 17), although differences other than age distribution in the Whitehall II study population from that of CFAS (67% male compared to 44% in CFAS; 48% O-level or lower educational attainment compared to 27% in CFAS), mean that this figure is approximate. The 463 cases ascertained to date in Whitehall II therefore suggests that 89% of those projected to have dementia have been diagnosed, which is higher than the national average. This may be because of the differences between Whitehall and CFAS populations I described above, but may also indicate that the Whitehall II population have higher health-seeking behaviours, perhaps because civil servants are more likely to use the NHS or because they are alerted to cognitive difficulties by repeated testing as part of the study.

I discussed in sections 5.4.5 and 6.2.2.2.1 the potential systematic bias in dementia ascertainment using electronic health records. Unmarried people have been shown to be less likely to receive dementia diagnosis (Sommerlad et al., 2018a, Savva and Arthur, 2015). It is possible that this extends to people with less frequent social contact as they may not have an informant who recognises emerging dementia

symptoms, encourages clinic attendance, and is able to give a collateral history to healthcare professionals assessing the patient. This is likely to result in some measurement bias, whereby the association between social contact and incident dementia is underestimated.

6.4.4 Chance

I conducted several different significance tests in this study, and multiple testing raises the risk of chance finding. The lack of consistent evidence at all time-points makes it more likely that the association found from age 60 years is a chance finding, although as I discussed in section 6.4.2.1, point estimates of the hazard ratio at each age point were similar. Some have argued that the threshold for accepting statistical significance should be adjusted to account for multiple testing, such as through use of Bonferroni correction (Dunn, 1961). However, as recommended by other authors (Perneger, 1998), I did not do so in my study, as the different tests I performed were complementary to my overall examination of the influence of social contact on cognition, and such approaches increase risk of type 2 error.

6.4.5 Selection and attrition bias

The initial response rate in this study was relatively high; 73% of those who were initially invited to participate took part in the study. However, selection bias is possible. Analysis of participants in the UK Biobank study, compared to nationally representative data sources, indicated that those who are older and from lower socioeconomic groups and those with less healthy lifestyle behaviours are under-represented (Fry et al., 2017). Participation in the Cognitive Function and Aging II Study was less likely for women and those from lower socioeconomic groups (Gao et al., 2015). I could not compare Whitehall II study participants to non-respondents but non-response bias may have been similar, meaning that those with lower level of social contact and at higher risk of dementia are more likely to have refused participation, resulting both in possible underestimation and loss of power to find association.

Attrition in the Whitehall II study has been low, with 80-90% of eligible people participating at each successive study wave. I found that non-participation was associated with lower level of social contact, but not with subsequent dementia incidence, with an advantage of the use of electronic records to ascertain dementia status being that we could collect outcome information about those who did not participate. Missing social contact data in successive study phases was associated both with lower baseline social contact and dementia risk, which may also have resulted in underestimation of the association.

My use of inverse probability weighting allowed me to estimate the association between social contact and dementia at different ages, taking into account the likelihood of study participation and complete data of the baseline study participants. My weighting included information about sociodemographic features, social network contact and dementia risk, making direct comparison between results at different ages possible. Weighted and unweighted results were similar at age points 50 and 60 years, when the numbers of included participants (8,487 and 7,439 respectively) were relatively close to the original study population of 10,308. However at age 70 years, when only 4,888 participated and gave social contact data, the unweighted results may have under-estimated the association (unweighted HR = 0.95, compared to weighted HR = 0.91), indicating the benefit of accounting for attrition and missing data in these analyses.

Cognitive data was more likely to be missing in people with less social contact and more likely to be missing for those who subsequently developed dementia. This suggests that the association between social contact and cognitive change is underestimated as those with dementia would be expected to have worse cognition and faster cognitive decline, as I found in my analysis stratified by subsequent dementia status. However, my use of mixed linear models in this analysis ensured that I was able to include data from all participants whose cognition was assessed at any time during follow-up, thereby minimising the effect of missing data.

Overall, there is therefore evidence that selection, attrition, and missingness bias may have resulted in underestimation of the associations found in my study, although analytic strategies of using inverse probability weighting and mixed linear models may have reduced the effect of these biases.

6.4.6 Confounding

My findings were independent of the known potential confounding effect of several lifestyle factors, health behaviours, and sociodemographic characteristics. I aimed to control for all potential confounding factors. I pre-specified potentially important confounders and chose included covariates after considering associations within my data, examining previously published evidence, and considering temporality of associations (section 6.3.5). There may, however, be unmeasured confounders which affect the reported associations.

I chose to not adjust analyses for mental health symptoms as a previous study using this cohort found that mental health symptoms, including depressive symptoms, did not predict dementia incidence (Singh-Manoux et al., 2017). As discussed in section 6.4.2.4 elevated level of stress is a potential mechanism by which low level of social contact could affect cognition and dementia risk, so adjusting for mental health symptoms may obscure the association. I also chose not to adjust for specific physical illnesses such as diabetes, hypertension, cardio- and cerebrovascular diseases, as I instead included health behaviours (smoking, alcohol use and physical activity) which are strong predictors of these diseases. My analyses examined people at relatively young age when prevalence of these conditions is low (Feigin et al., 2003, Isomaa et al., 2001), whereas potentially harmful health behaviours were more common at these ages. I therefore judged that adjusting for the conditions may be insufficient, whereas adjusting for causative health behaviours would better address the potential confounding effect of physical ill-health.

There are some potential confounding variables that were unavailable in the Whitehall study. Hearing impairment is an emerging risk factor for dementia (Wei et al., 2017) which is not objectively measured in the Whitehall II study. Hearing could

potentially confound the association between social contact and dementia or it may be that reduced social contact is on the causal pathway by which hearing impairment affects dementia risk. There is also emerging evidence that environmental pollution and head injuries are risk factors for dementia, and these factors could be associated with social contact frequency and therefore confound the association, but accurate measures are not available in Whitehall II.

Finally, my analytic approach did not address the potential competing risk of death in the association between social contact and dementia. Low social contact is associated with increased mortality (Holt-Lunstad et al., 2010), so death may occur earlier in people with low social contact meaning that they have had less time to develop dementia, therefore underestimating the association of social contact with dementia. However, my analytic approach using Cox regression is appropriate as it takes account of follow-up time. Secondly, the cohort was relatively young with low mortality rates (only 16% of the cohort had died by end of follow-up). Thirdly, dementia cases were ascertained from mortality data which, although limited in its sensitivity to identify dementia, is becoming increasingly accurate over time (Perera et al., 2016b). This means that some cases were diagnosed at death or post-mortem, maximising the detection of dementia in the deceased members of the cohort. In addition, as recommended by previous literature, my study adjusted for potential confounders of the social contact-death relationship (e.g. age, sex, health behaviours) which has the effect of reducing bias due to competing risks (Lesko and Lau, 2017).

Overall, I cannot rule out any residual confounding which may have increased the associations I report in my study, but found little evidence for confounding in my analyses using other potential confounders.

6.4.7 Reverse causation bias

The long duration of follow-up between measurement of social contact frequency at age 60 and dementia (mean 14.6 years) suggests that reverse causation bias does not underpin the association found at this age. As discussed previously (section 6.4.2.2)

prodromal symptoms of dementia are unlikely to emerge this long in advance of dementia diagnosis. This is strengthened by the negative findings from my analysis of the association between change in social contact from age 60 to 70 years and dementia incidence over the subsequent 7.5 years (section 6.3.7). If the association found at age 60 was due to emergent dementia pathology causing decline in social contact, then we would expect people who declined in social contact to be at highest risk of dementia, but this was not the case. This analysis may have been underpowered as only 855 people were in the 'decreasing social contact' category, of whom 40 (4.7%) developed dementia but there was no indication in the point estimate from this analysis (HR for decreasing social contact compared to 'remaining high' = 1.07 (0.63, 1.82)) that this was a high-risk group.

Examining the direction of causality between lifetime social contact and cognitive reserve was not an aim of my study, as doing so in detail would likely require data on social contact from adolescence to be able to examine the temporality between social and cognitive function. However, the results of my study have provided some preliminary evidence regarding the direction of this association, although these need to be interpreted with caution.

I have previously argued that social contact may act to reduce dementia risk through its effect on building greater cognitive reserve (section 6.4.2.4). However, any relationship between social contact and cognition could alternatively be interpreted as higher cognitive ability causing higher level of social contact, as outlined in section 2.3.1. This explanation would suggest that higher childhood and adolescent cognitive ability allows individuals to develop and maintain more frequent social contact, meaning that social contact may part-mediate the association between cognitive reserve and subsequent dementia risk. In addition, childhood cognitive abilities have been inversely associated with risk of mental health symptoms (Martin et al., 2007), which could also mediate the association between cognitive reserve and dementia risk as, for example, anxiety symptoms may adversely affect attention (Bishop, 2009) and other cognitive domains.

The explanation that social contact may be a consequence, rather than cause of cognitive reserve, may be supported from my finding that higher social contact (combined friends and relatives) from age 45 to 55 years is associated with greater baseline cognitive function at 55 but not with subsequent cognitive change, and that more frequent contact with friends is actually associated with slightly faster cognitive decline (0.03 standard deviations per 10 years for the highest tertile of social contact compared to the lowest).

However, my analyses were adjusted for level of education and socioeconomic status defined by employment grade, which are among the most widely used and consistent measures of cognitive reserve. This association of greater mean social contact during 10 years with higher cognition may therefore have been independent of baseline cognitive reserve. If so, this would suggest that social contact during these years, which may also reflect social contact preceding the first Whitehall II assessment, builds greater cognitive function which is subsequently maintained. Previous studies have largely reported similar findings; that markers of higher cognitive reserve are associated with higher baseline cognition, and that differences in cognition between those with high and low cognitive reserve are maintained, but not increased, during follow-up. I will discuss this further in the context of other literature in more detail in section 6.4.9.2.

6.4.8 Generalisability of study findings to general population

The Whitehall II study was established as an occupational, rather than population, cohort. Participants were derived from one very large employer, the UK civil service, and based in London originally (Marmot and Brunner, 2005), so do not reflect the general employment structure of the UK as no study participants were unemployed at baseline, and manual occupations are underestimated. However, trends in employment in the UK mean that there are fewer manual workers and jobs are predominantly office-based and technology-focused, which the Whitehall participants may more closely resemble (Holmes and Mayhew, 2012). Women are underrepresented, as they form only one third of the cohort, and half of them were from clerical and office support employment grades. People from ethnic minorities

are slightly underrepresented with 89% of Whitehall participants who are White, compared to 86% in the UK at latest census (Office for National Statistics, 2016).

I tested for effect modification by gender on the association of social contact with dementia and did not find any evidence for this. There is no clear plausible explanation for different socio-economic grades or ethnic groups modifying the effect of social contact on dementia, so I do not expect that these differences in Whitehall II cohort from the UK general population would have affected the estimate of the association in my study. However, testing the replicability of my findings in other settings will be of use and I have made provisional plans to do so in the Longitudinal Aging Study Amsterdam (Huisman et al., 2011).

The participants of the Whitehall II study are relatively young for evaluation of dementia. Just under half of participants were aged over 75 years at the end of follow-up and this means that the mean age at diagnosis was 75.9 years (minimum 56.9 years), which compares to the age at diagnosis of participants in my study of all people diagnosed with dementia in four South London boroughs between 2008-16 (Chapter 5), which was 82.2 years. The relatively young age of participants in this study may have affected the association found between social contact and dementia. Younger onset dementias have a larger relative genetic contribution (Rossor et al., 2010), meaning that the influence of lifestyle factors on dementia aetiology in these groups is likely to be smaller. Therefore, my study may underestimate risk of low social contact for a whole general population at risk of dementia. Further examination of this will be possible when replicating my analyses in another cohort, and potentially by repeating my analyses in future.

Finally, the global applicability of my findings are unclear as the nature of social contact varies widely in different settings. We conducted a study of the population attributable fraction of established dementia risk factors in eight different countries, using data from the 10/66 study (Prince et al., 2007). We found that prevalence of low social contact, defined as self-reported contact frequency with friends, relatives and neighbours or attendance at social clubs occurring less than monthly in later-life,

varied from 0.5% in six Latin American countries, to 3.4% in China, and 10.4% in India (Mukadam et al., 2019). Methodology for measuring social contact was the same across these countries, though there is likely to be measurement error in these findings. This range in social contact would mean that the potential impact of infrequent social contact would vary widely between different countries, and if the nature of social contact differs in these settings, then the relative risk associated with social contact may also vary. Replicating my analyses may therefore be desirable in a range of different settings, rather than simply in Western societies.

6.4.9 Comparison of findings with previous studies

6.4.9.1 Social contact and dementia

The magnitude of effect in my study was markedly smaller than has been found in most previous studies. The pooled estimate from the recent meta-analysis of this association (inverted to reflect comparison of high v low, rather than low v high social contact) was 0.64 (0.54, 0.76), although this figure combined estimates from heterogenous comparator groups. The figure from my study indicates 12% reduction in dementia incidence for each standard deviation higher social contact score at age 60 years. Standard deviation on this scale was 3 points, equivalent to, for example, the difference between seeing 1-2 friends or acquaintances once every few months compared to seeing 1-2 people almost daily.

A study of older US women with up to 4 years follow-up reported risk of dementia for those having daily, compared to less than weekly, contact, which is an analogous comparison to that in my study, to be 43% lower (Crooks et al., 2008); this estimate was adjusted for age, education, health, and baseline cognition. Having daily compared to no contact with relatives and friends in a Swedish study with 3 years of follow-up was associated with 29% reduced incidence of dementia in age, sex and education-adjusted models (Fratiglioni et al., 2000). The only previous study which had greater than 4 years of follow-up compared rates of dementia in Chinese people aged over 55 years who 'visited friends' to those who did not (He et al., 2000). No further detail was given in this study on how these binary categories were generated, but a surprisingly high three-quarters of study participants did not 'visit friends'. The

age and sex-adjusted risk of dementia in people who reported that they visited friends 10 years earlier was 37% lower than those who did not.

The lower estimate in my study is likely to be a consequence of one or both of overestimation of the effect by previous studies, and underestimation by my study. Previous studies may overestimate the association due to reverse causation bias because of short follow-up, and insufficient adjustment for confounders. My study may underestimate the association because of response bias related to non-participation of those with lower social contact, ascertainment bias related to use of electronic health records, and the study population being relatively young therefore reducing the influence of lifestyle compared to genetic factors.

6.4.9.2 Social contact and cognitive function

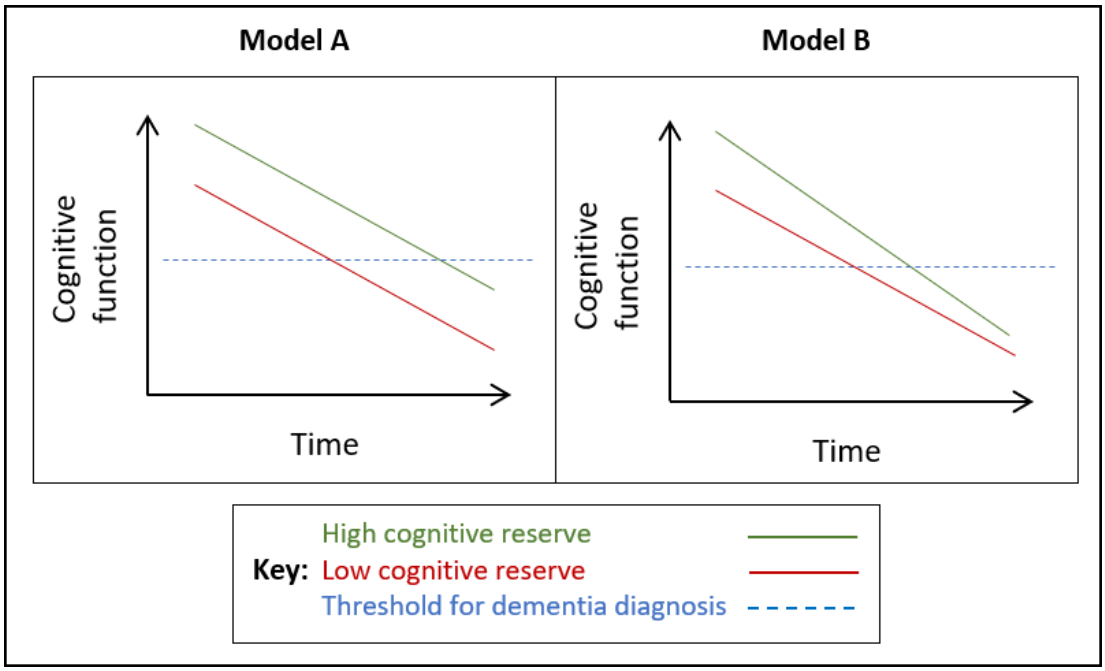
The overall mean cognitive decline in this study of 0.4 standard deviations per 10 years from age 55 during mean 14.3 years follow-up is consistent with that found in other studies of participants of similar age. A cohort of 13,351 US adults with mean 57 years at baseline declined in composite cognitive score by 0.78 standard deviations over 20 years, which is closely consistent with my findings (Rawlings et al., 2014). Another cohort of people aged 25 years at baseline, declined in cognition by around one standard deviation in women and one third of a standard deviation in men over subsequent mean 28 years (Willis and Schaie, 1999). Studies of older participants have found that older groups experience faster cognitive decline. Cognitive function of UK adults aged over 75 years declined by 0.65 standard deviations during 4 years follow-up (Cullum et al., 2000), and cognition declined by 0.52 standard deviations during 5.6 years follow-up in US adults with mean age 82 years (Scarmeas et al., 2006).

6.4.9.2.1 Cognitive reserve

Previous studies of cognitive reserve have reported findings consistent with two models which I have illustrated in Figure 6-7. Model A proposes that cognitive reserve reflects the persistence of earlier differences in cognitive functioning rather than differential rates of age-associated cognitive decline; higher reserve confers cognitive

benefit, and this benefit is constant over time. Model B suggests that higher reserve leads to greater initial cognitive abilities, but that cognitive decline is faster in this group. This may be 1) because cognitive loss over time is proportional to the level of baseline cognition; 2) because of floor effects in some tests meaning lesser decline in those with low baseline cognition; or 3) because people with high cognitive reserve have higher neuropathology than those with lower cognitive reserve by the time the begin to develop dementia. In both models A and B, reaching dementia threshold is delayed in those with higher cognitive reserve.

Figure 6-7: Theoretical models of cognition over time, according to cognitive reserve



I did not specifically aim to examine cognitive reserve in this study, but I will discuss the findings of my analysis of the association of social contact between 45-55 years with baseline cognition at 55 years and subsequent cognitive change, in the context of these theoretical models and previous research. The findings from most of my analyses were consistent with model A. I only found results consistent with model B in analysis of contact with friends and combined cognition, where those with high v low tertiles of social contact had slightly faster cognitive decline (0.03 standard deviations per 10 years). However, the differences were small and these findings were not consistent across individual cognitive tests.

Several other studies examining education as a marker of cognitive reserve and subsequent cognitive decline have reported findings consistent with model A. One study of 690 US adults aged between 60 and 89 years at baseline, using years of education and vocabulary ability as markers of cognitive reserve, found an association with baseline level of cognition but not with change in cognitive function (Tucker-Drob et al., 2009). Another study of people aged over 75 years in the UK found that level of education was associated with baseline cognitive function but not change in cognition (Muniz-Terrera et al., 2009).

Studies examining potential dementia risk factors other than education which may contribute to cognitive reserve, such as leisure activities, have also reported findings consistent with model A from Figure 6-7. A study of 2,854 participants in a French cohort found that social, intellectual and physical activities were associated with higher baseline cognition but not with subsequent rate of change, and was also associated with reduced rate of subsequent dementia (Marioni et al., 2015). Participation in leisure activities was associated with cognition but not cognitive decline from age 43 to 53 in a study using UK cohort data (Richards et al., 2003).

We previously examined the association of a range of structural measures of social relationships (i.e. amount of participation in social relationships) and different trajectories of cognition generated using latent class growth analysis (Greene and Hensher, 2003), using all but the most recent phase of Whitehall II data (Elovainio et al., 2017b). The three cognitive trajectory groups yielded from this model were consistent with model A as they had differing levels of baseline cognition and only very small differences in the slope between cognitive trajectories. We examined whether marital status and combined social contact, measured at one study phase, was associated with subsequent cognitive trajectory group, finding that higher social contact was associated with lower risk of subsequent low cognitive trajectory, in analyses adjusted for socioeconomic status but not education. The current study is a different analysis, as I used mean social contact over 10 years, longer duration of cognitive follow-up, and a different modelling approach, including adjustment for level of education.

In contrast to the studies which support model A, a previous analysis of cognitive function in the Whitehall II cohort reported findings consistent with model B for the association of occupational status and cognition, finding that higher status occupations were associated with higher baseline cognition but with slightly faster cognitive decline (Singh-Manoux et al., 2011). Height and education, also used as potential markers of cognitive reserve were not associated with rate of decline, and therefore supported model A. The authors speculated that the association of higher status occupations with faster cognitive decline may result from any cognitive benefit from occupation being only transient, although no studies have replicated this finding, so we cannot be certain of this hypothesis.

Two other studies have reported findings consistent with model A for people who do not develop dementia, and with model B for those who do develop dementia, as indicated in my analysis stratified by dementia status of the association between social contact and cognitive decline (Appendix 16). In one study, three markers of socioeconomic status (height, education and occupational status) were associated with baseline cognition but not cognitive change in people who did not develop dementia and with faster cognitive decline in those who did develop dementia (Rusmaully et al., 2017). A study of 350 US adults with mean age 57 years at baseline were grouped as high and low cognitive reserve, according to level of education, reading ability, and vocabulary. People who did not develop dementia had different levels of baseline cognitive ability but did not differ in their cognitive trajectories, whereas people with high cognitive reserve who went on to develop dementia had significantly faster cognitive decline than the dementia cases with low cognitive reserve (Soldan et al., 2017).

Taken together, the findings from these analyses suggest that high cognitive reserve reflects early and persistent differences in cognition compared to those with low cognitive reserve, rather than protection against the rate of decline. The relationship is different for cognitive change in prodromal dementia, whereby decline is faster for those with higher cognitive reserve. Findings from my study are consistent with these overall models and, importantly, persist following adjustment for education and

socioeconomic status which are traditional markers of cognitive reserve. This gives some evidence that social contact confers increased cognitive reserve in addition to these other factors. However, this was not a primary aim of my study and the strength of evidence is limited by only being able to examine social contact from mean age 45 years onwards, so not being able to specifically consider longitudinal associations between social contact and cognition from childhood, when cognitive reserve probably begins to be built (Richards and Sacker, 2003). Potential approaches to examine this in more detail in future include examining younger cohorts with long follow-up duration and multiple assessment of social and cognitive function, and by attempts to adjust analyses for baseline cognitive function, such as by using educational measures such as reading ability (Nelson and Willison, 1991).

6.4.10 Conclusions

In this study, I found that more frequent social contact at age 60 years was associated with reduced risk of dementia, although I did not find evidence for association at age 50 and 70 years. I found that the association is unlikely to be due to the reverse causation which may have affected previous studies, and that social contact is associated with higher cognition but not rate of cognitive decline. This study of the association between social contact and dementia and cognition has several important strengths which mean that the conclusions from my study are stronger than those of previous research. I have followed STROBE reporting guidelines for reporting observational studies (Elm et al., 2007) and have also considered and addressed recommendations from an expert working group on conduct of studies relating to population research on dementia risk (Weuve et al., 2015).

On balance, I consider that my results suggest that frequency of social contact is a risk factor for dementia. Although associations were only statistically significant at one age point and not two others, the estimate of association was similar at all three ages, and the finding of social contact being associated with higher baseline cognition is consistent with other studies of established risk factors and potentially consistent with cognitive reserve being the mechanism for a protective effect of social contact. The limitations I have identified relating to selection bias, attrition bias, and

measurement bias from the dementia ascertainment method may all have resulted in underestimation of the association and error in measurement of social contact is likely to have reduced the power of my study to find significant results, so the association may be stronger than I have reported.

6.4.10.1 Clinical and research implications

There is need for identification of modifiable dementia risk factors and my study suggests that social contact in late middle-age reduces risk of subsequent dementia. My findings need replication in other large cohorts with long duration of follow-up and I have identified the Longitudinal Aging Study Amsterdam (Huisman et al., 2011) as one potential cohort with similar data. The preliminary evidence from my results that social contact may build cognitive reserve also need further exploration in future studies, by attempting to improve estimation of cognitive reserve, as discussed in section 6.4.9.2.1.

6.4.10.1.1 Implications for clinical interventions

If social contact were a causal factor for dementia, it would be a potentially-modifiable target for preventative intervention studies. However, there are numerous challenges with developing effective social interventions. Firstly, the modifiability of social contact is unclear meaning that there is limited evidence for any intervention successfully addressing social isolation (Health quality Ontario, 2008). An intervention which encourages increased social contact would need to be acceptable to study participants, feasible to administer, and sustainable in order to potentially have effect. Secondly, my strongest findings related to people aged 60 years, who would require many years or decades of follow-up to be able to assess dementia risk with confidence, and this is impractical. Therefore any potential future intervention may need to assess cognitive change, rather than dementia incidence, as a primary outcome with secondary examination of effects on functional ability. I will discuss previous interventions in more detail below.

As previously discussed, social changes occur in early dementia (Ismail et al., 2016, Budgett et al., 2019), and my findings from this study of the influence of social contact

on cognition and dementia are consistent with the potential existence of a bidirectional relationship in prodromal and early dementia, although I did not examine the prodromal phase in detail in this study. This would suggest that there may be particular value in intervening in preclinical dementia, at a time when loss of social contact may be occurring as part of the disease, and perpetuating disease progression.

Some studies suggest a beneficial effect of social contact in early dementia. Cognitive stimulation therapy administered in groups to people with dementia resulted in improved cognition (Spector et al., 2003) and is now part of NICE guidelines for people with dementia (Pink et al., 2018). However, a very similar intervention delivered one-to-one was not (Orrell et al., 2017), which may suggest that part of the mechanism for group cognitive stimulation therapy improving cognition is through increasing social contact. Another recent feasibility study examined the effect of daily internet-based conversational interactions on cognitive decline in people with mild cognitive impairment. It reported that acceptability of the interview to participants was high, attrition was low, and that there was better verbal fluency at 12 week follow-up in those who received the intervention compared to the control group (Dodge et al., 2015). Though this study was single-blinded and with short duration of follow-up, it provides some guidance on a potentially feasible and acceptable intervention and suggests that effect may be seen when delivered to those with a prodromal dementia state.

Therefore, any future clinical intervention would need to develop a feasible and acceptable intervention and test it in a randomised controlled trial over a longer period of follow-up. Considering that blinding participants to whether they are participating in a social intervention is challenging, so any intervention may be single-blind, whereby only the outcome assessor is unaware whether study participants are randomised to intervention or control. However, it may be possible to also blind study participants, by careful design of a credible control condition and by not actively disclosing group allocation to participants. Considering that the strongest evidence for reducing cognitive decline comes from multidomain interventions which

combine a number of different aspects (Kane et al., 2017), incorporating social contact into other multidomain interventions may be an appropriate strategy.

The findings of some trials of social interventions (Mann et al., 2017) on other health outcomes have yielded encouraging results. One study of peer support, consisting of proactive individualised telephone based contact from mother to mother, aimed at promoting social support to women identified as at high risk for postnatal depression (Dennis et al., 2009) led to lower depressive symptoms. However cognitive behavioural therapy aimed at promoting social support as part of treatment after heart attack (Berkman et al., 2003) or stroke (Ellis et al., 2010), and befriending interventions in dementia (Charlesworth et al., 2008), have failed to find beneficial effects on their primary intended outcomes.

For middle and early-old age general population, such research-led interventions are likely to be excessively intensive and expensive, and unacceptable as they do not resemble the experiences and interactions which occur naturally in social relationships. Therefore, supporting people to be more socially active and make use of existing relationships, rather than merely attempting to provide new social contacts, may be more appropriate approaches for interventions.

6.4.10.1.2 Implications for public health interventions

It may be that less intensive, but more widely disseminated public health measures are potential avenues for increasing social contact in a general population. In the UK, Public Health England have made recommendations on how to reduce dementia risk which include encouraging 'connection with people' and community-level recommendations of 'interventions to address healthy lifestyles [and] social isolation' (Public Health England, 2018). The increasing public discourse on loneliness in older people (The Guardian, 2017, Age UK, 2015) as well ongoing work on health promotion approaches to loneliness and social isolation (Landeiro et al., 2017), may drive a reversal of the trend towards more isolated older communities (McPherson et al., 2006). Public health measures aiming at social inclusion and increased community connectedness have potential for impact on cognition and dementia risk.

6.4.10.1.3 Summary

Considering the general health benefits, described in section 2.2.3, associated with good quality social relationships, and the lack of known adverse effects, people at risk of developing dementia should be encouraged to try to increase social contact with others. Potential public health approaches to reducing isolation in older people and increasing societal connectedness may be beneficial and future research on clinical interventions should test the feasibility of increasing social contact and its effect on cognition and dementia risk.

Chapter 7: **Conclusions**

The rising number of people with dementia globally has led to pressing need for identification of potentially modifiable risk factors which can be targeted at individual and population level. Preliminary evidence suggested that more social contact may be associated with lower dementia risk, but limitations in previous studies meant that this association was unclear, so I aimed to examine this in more detail in my thesis.

In my meta-analysis, I found evidence that being married, used as a proxy marker for greater cumulative social contact, is associated with lower dementia risk independent of age, sex, educational status, and physical health. I published a peer-reviewed paper reporting these findings and disseminated the results widely through avenues including conference presentation, television and radio interviews, podcast, and public engagement events.

I then conducted a cohort study using data from the Whitehall II study of UK civil servants, finding evidence that more frequent social contact is associated with slightly lower dementia risk, and some evidence for a potential mechanism through higher level of cognition. These associations were also independent of sociodemographic, health, and lifestyle factors. This study is novel as it has the longest duration of follow-up of any previous study thereby strengthening the evidence, and has elucidated potential explanations for the previously reported association.

In addition, I conducted a study of the validity of electronic health records for ascertaining dementia status using two UK routine data sources. I reported for the first time the sensitivity and specificity of dementia diagnosis in the Hospital Episode Statistics database, which informed my subsequent use of these data in my analysis of the Whitehall II cohort. This study also identified clinical and sociodemographic predictors of accurate dementia recording which informs research use of this data-source for dementia status ascertainment, and also clarified current clinical practice and inequities in dementia diagnosis in general hospitals. I published two research

papers using these data and discussed the implications of my findings on national television and radio.

7.1 Future directions

During the course of my PhD, I have gained experience in systematic review and meta-analysis; longitudinal data analysis including logistic and Cox regression and multilevel modelling; dealing with missing data using multiple imputation and inverse probability weighting; interpreting results; and academic writing. I have addressed the primary outcomes of my own study and have gained further experience in handling large databases. I have also undertaken other research studies using these skills. The PhD has led to UK and international collaborations and an expansion of my research interests.

I plan further epidemiological studies examining my findings from this thesis in more detail using collaborations built during my PhD. I intend to repeat my analysis of the association of social contact frequency and dementia and cognition in other cohorts, specifically Longitudinal Aging Study Amsterdam (Huisman et al., 2011), to examine the replicability and generalisability of my findings, and the potential effect of social contact on cognitive reserve in more detail. I intend to examine potential mechanisms underlying the association between widowed marital status and dementia by comparing cognitive trajectories in people who were recently widowed to those who have longer-term widowed status, using data from the Whitehall II study (Marmot and Brunner, 2005) and the Brazilian Longitudinal Study of Adult Health (Schmidt et al., 2014). If cognition is worse in people with long-term widowhood, this may suggest that low social contact is a potential mechanism, whereas if those recently bereaved experience faster cognitive decline, then emotional stress of bereavement may underpin this association.

My work on hospital admission of people with dementia and recognition of dementia in hospitals has also sparked my interest in the interface between community and hospital care. I intend to examine potentially modifiable targets for hospital admissions in older people with dementia using the Adult Changes in Thought Study

(Montine et al., 2012) and will travel to Seattle, US, in July 2019 to begin work on this cohort. I am also a co-applicant on a Programme Development Grant application which proposes to develop an intervention to reduce hospitalisation in people newly diagnosed with dementia, working towards testing in a randomised controlled trial.

My long term aim is to translate observational findings into testable interventions. I therefore intend to use my epidemiological study evidence to identify modifiable targets in priority areas, inform intervention development, and use methodological and statistical skills gained during the course of this PhD to evaluate their efficacy. I look forward to developing and leading new programmes aiming to bring benefit to the public, and improve quality of life for people living with dementia and their families.

References

ADAMS, R. G. & BLIESZNER, R. 1995. Aging well with friends and family. *American Behavioral Scientist,* 39**,** 209-224.

ADELBORG, K., HORVÁTH-PUHÓ, E., ORDING, A., PEDERSEN, L., TOFT SØRENSEN, H. & HENDERSON, V. W. 2017. Heart failure and risk of dementia: a Danish nationwide population-based cohort study. *European journal of heart failure,* 19**,** 253-260.

ADELMAN, S., BLANCHARD, M., RAIT, G., LEAVEY, G. & LIVINGSTON, G. 2011. Prevalence of dementia in African–Caribbean compared with UK-born White older people: two-stage cross-sectional study. *The British Journal of Psychiatry,* 199**,** 119-125.

AGE UK 2015. Evidence Review: Loneliness in Later Life - Age UK. London.

AHMADI-ABHARI, S., GUZMAN-CASTILLO, M., BANDOSZ, P., SHIPLEY, M. J., MUNIZ-TERRERA, G., SINGH-MANOUX, A., KIVIMÄKI, M., STEPTOE, A., CAPEWELL, S. & O'FLAHERTY, M. 2017. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. *British Medical Journal,* 358**,** j2856.

AMERICAN PSYCHIATRIC ASSOCIATION 2000. *DSM-IV-TR: Diagnostic and statistical manual of mental disorders, text revision,* Washington, DC, American Psychiatric Association.

AMIEVA, H., LE GOFF, M., MILLET, X., ORGOGOZO, J. M., PÉRÈS, K., BARBERGER-GATEAU, P., JACQMIN-GADDA, H. & DARTIGUES, J. F. 2008. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 64**,** 492-498.

AMIEVA, H., STOYKOVA, R., MATHARAN, F., HELMER, C., ANTONUCCI, T. C. & DARTIGUES, J.-F. 2010a. What aspects of social network are protective for dementia? Not the quantity but the quality of social interactions is protective up to 15 years later. *Psychosomatic Medicine,* 72**,** 905-911.

AMIEVA, H., STOYKOVA, R., MATHARAN, F., HELMER, C., ANTONUCCI, T. C. & DARTIGUES, J. F. 2010b. What aspects of social network are protective for dementia? Not the quantity but the quality of social interactions is protective up to 15 years later. *Psychosom. Med,* 72**,** 905-911.

ARAI, A., KATSUMATA, Y., KONNO, K. & TAMASHIRO, H. 2004. Sociodemographic factors associated with incidence of dementia among senior citizens of a small town in Japan. *Care Management Journals,* 5**,** 159-65.

ARVANITAKIS, Z., WILSON, R. S., BIENIAS, J. L., EVANS, D. A. & BENNETT, D. A. 2004. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Archives of neurology,* 61**,** 661-666.

AVISON, W., MCLEOD, J. & PESCOSOLIDO, B. 2007. *Mental Health, Social Mirror,* New York, Springer.

AWORINDE, J., WERBELOFF, N., LEWIS, G., LIVINGSTON, G. & SOMMERLAD, A. 2018. Dementia severity at death: a register-based cohort study. *BMC psychiatry,* 18**,** 355.

AYLIN, P., ALEXANDRESCU, R., JEN, M., MAYER, E. & BOTTLE, A. 2013. Day of week of procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics. *British Medical Journal,* 346**,** f2424.

BAE, J. B., KIM, Y. J., HAN, J. W., KIM, T. H., PARK, J. H., LEE, S. B., LEE, J. J., JEONG, H. G., KIM, J. L., JHOO, J. H., YOON, J. C. & KIM, K. W. 2014. Incidence of and risk factors for Alzheimer's disease and mild cognitive impairment in Korean elderly. *Dementia and Geriatric Cognitive Disorders,* 39**,** 105-115.

BAILEY, P. E., HENRY, J. D. & VON HIPPEL, W. 2008. Empathy and social functioning in late adulthood. *Aging Ment Health,* 12**,** 499-503.

BARBERGER-GATEAU, P., RAFFAITIN, C., LETENNEUR, L., BERR, C., TZOURIO, C., DARTIGUES, J.-F. & ALPÉROVITCH, A. 2007. Dietary patterns and risk of dementia The Three-City cohort study. *Neurology,* 69**,** 1921-1930.

BEARD, C., KOKMEN, E., OFFORD, K. P. & KURLAND, L. T. 1992. Lack of association between Alzheimer's disease and education, occupation, marital status, or living arrangement. *Neurology,* 42**,** 2063-2068.

BENEDICT, R. H., SCHRETLEN, D., GRONINGER, L. & BRANDT, J. 1998. Hopkins Verbal Learning Test–Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist,* 12**,** 43-55.

BENNETT, D., SCHNEIDER, J., ARVANITAKIS, Z., KELLY, J., AGGARWAL, N., SHAH, R. & WILSON, R. 2006a. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology,* 66**,** 1837-1844.

BENNETT, D. A., SCHNEIDER, J. A., TANG, Y., ARNOLD, S. E. & WILSON, R. S. 2006b. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *The Lancet Neurology,* 5**,** 406-412.

BERKMAN, L. F., BLUMENTHAL, J., BURG, M., CARNEY, R. M., CATELLIER, D., COWAN, M. J., CZAJKOWSKI, S. M., DEBUSK, R., HOSKING, J. & JAFFEE, A. 2003. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA: Journal of the American Medical Association,* 289**,** 3106-16.

BERKMAN, L. F. & SYME, S. L. 1979. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *American journal of Epidemiology,* 109**,** 186-204.

BICKEL, H. & COOPER, B. 1994. Incidence and relative risk of dementia in an urban elderly population: findings of a prospective field study. *Psychological Medicine,* 24**,** 179-92.

BIRD, C. M., PAPADOPOULOU, K., RICCIARDELLI, P., ROSSOR, M. N. & CIPOLOTTI, L. 2004. Monitoring cognitive changes: Psychometric properties of six cognitive tests. *British Journal of Clinical Psychology,* 43**,** 197-210.

BISHOP, S. J. 2009. Trait anxiety and impoverished prefrontal control of attention. *Nature neuroscience,* 12**,** 92.

BOILER, F., LOPEZ, O. L. & MOOSSY, J. 1989. Diagnosis of dementia Clinicopathologic correlations. *Neurology,* 39**,** 76-76.

BRILLEMAN, S. L., PACHANA, N. A. & DOBSON, A. J. 2010. The impact of attrition on the representativeness of cohort studies of older people. *BMC medical research methodology,* 10**,** 71.

BROUWERS, N., SLEEGERS, K. & VAN BROECKHOVEN, C. 2008. Molecular genetics of Alzheimer's disease: an update. *Annals of medicine,* 40**,** 562-583.
BROWN, A., KIRICHEK, O., BALKWILL, A., REEVES, G., BERAL, V., SUDLOW, C., GALLACHER, J. & GREEN, J. 2016. Comparison of dementia recorded in routinely collected hospital admission data in England with dementia recorded in primary care. *Emerging themes in epidemiology,* 13**,** 11.
BRUGHA, T. S., STURT, E., MACCARTHY, B., POTTER, J., WYKES, T. & BEBBINGTON, P. E. 1987. The Interview Measure of Social Relationships: the description and evaluation of a survey instrument for assessing personal social resources. *Soc Psychiatry,* 22**,** 123-8.
BUDGETT, J., BROWN, A., DALEY, S., PAGE, T., BANERJEE, S., LIVINGSTON, G. & SOMMERLAD, A. 2019. The social functioning in dementia scale (SF-DEM): Exploratory factor analysis and psychometric properties in mild, moderate and severe dementia. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring,* 11**,** 45-52.
BURNS, A., NHS ENGLAND, WILKINSON, A. & PEACHEY, S. 2014. Best practice in Memory Services: Learning from across England. London.
BURNS, E. M., RIGBY, E., MAMIDANNA, R., BOTTLE, A., AYLIN, P., ZIPRIN, P. & FAIZ, O. 2011. Systematic review of discharge coding accuracy. *Journal of public health,* 34**,** 138-148.
CAMPBELL, K. E. & LEE, B. A. 1992. Sources of personal neighbor networks: social integration, need, or time? *Social forces,* 70**,** 1077-1100.
CASSERLY, I. & TOPOL, E. J. 2004. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *The Lancet,* 363**,** 1139-1146.
CHAN, K. Y., WANG, W., WU, J. J., LIU, L., THEODORATOU, E., CAR, J., MIDDLETON, L., RUSS, T. C., DEARY, I. J. & CAMPBELL, H. 2013. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990–2010: a systematic review and analysis. *The Lancet,* 381**,** 2016-2023.
CHARLESWORTH, G., SHEPSTONE, L., WILSON, E., REYNOLDS, S., MUGFORD, M., PRICE, D., HARVEY, I. & POLAND, F. 2008. Befriending carers of people with dementia: randomised controlled trial. *British Medical Journal,* 336**,** 1295-1297.
CHEN, Q. & SCHUBERT, D. 2002. Presenilin-interacting proteins. *Expert reviews in molecular medicine,* 4**,** 1-18.
CHEN, R., HU, Z., WEI, L., MA, Y., LIU, Z. & COPELAND, J. R. 2011. Incident dementia in a defined older Chinese population. *PloS one,* 6**,** e24817.
CHEVALLIER, C., KOHLS, G., TROIANI, V., BRODKIN, E. S. & SCHULTZ, R. T. 2012. The social motivation theory of autism. *Trends in cognitive sciences,* 16**,** 231-239.
CHIONG, W., WILSON, S. M., D'ESPOSITO, M., KAYSER, A. S., GROSSMAN, S. N., POORZAND, P., SEELEY, W. W., MILLER, B. L. & RANKIN, K. P. 2013. The salience network causally influences default mode network activity during moral reasoning. *Brain,* 136**,** 1929-41.
COHEN, S. 2004. Social relationships and health. *American psychologist,* 59**,** 676.
CORDER, E. H., SAUNDERS, A. M., STRITTMATTER, W. J., SCHMECHEL, D. E., GASKELL, P. C., SMALL, G., ROSES, A. D., HAINES, J. & PERICAK-VANCE, M. A.

1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science,* 261**,** 921-923.
CORNWELL, B. 2011. Age trends in daily social contact patterns. *Research on Aging,* 33**,** 598-631.
CORREA RIBEIRO, P. C., DE SOUZA LOPES, C., ALVES LOURENCO, R. & RUBIO, M. M. 2013. Prevalence of dementia in elderly clients of a private health care plan: A study of the FIBRA-RJ, Brazil. *Dementia and Geriatric Cognitive Disorders,* 35**,** 77-86.
COX, D. R. 1972. Regression models and life-tables. *Journal of the Royal Statistical Society: Series B (Methodological),* 34**,** 187-202.
CROCKER, L. & ALGINA, J. 1986. *Introduction to classical and modern test theory*, Wadsworth Publishing Co.
CROOKS, V. C., LUBBEN, J., PETITTI, D. B., LITTLE, D. & CHIU, V. 2008. Social network, cognitive function, and dementia incidence among elderly women. *Am J Public Health,* 98**,** 1221-7.
CULLUM, S., HUPPERT, F. A., MCGEE, M., DENING, T., AHMED, A., PAYKEL, E. S. & BRAYNE, C. 2000. Decline across different domains of cognitive function in normal ageing: results of a longitudinal population-based study using CAMCOG. *International journal of geriatric psychiatry,* 15**,** 853-862.
CUNNINGHAM, H. 2002. GATE, a general architecture for text engineering. *Computers and the Humanities,* 36**,** 223-254.
DAHL, A., BERG, S. & NILSSON, S. E. 2007. Identification of dementia in epidemiological research: a study on the usefulness of various data sources. *Aging-Clinical & Experimental Research,* 19**,** 381-9.
DAHLBERG, L. & MCKEE, K. J. 2014. Correlates of social and emotional loneliness in older people: evidence from an English community study. *Aging & mental health,* 18**,** 504-514.
DAVIDSON, S. & ROSSALL, P. 2014. Evidence review: Loneliness in later life. *Age UK*.
DAVIGLUS, M. L., BELL, C. C., BERRETTINI, W., BOWEN, P. E., CONNOLLY, J. E., COX, N. J., DUNBAR-JACOB, J. M., GRANIERI, E. C., HUNT, G. & MCGARRY, K. 2010. NIH State-of-the-Science Conference Statement: Preventing Alzheimer's disease and cognitive decline. *NIH consensus and state-of-the-science statements,* 27**,** 1-30.
DEMENTIA PLATFORMS UK. 2019. *DPUK Data Portal* [Online]. Available: https://portal.dementiasplatform.uk/ [Accessed 2019].
DENNIS, C.-L., HODNETT, E., KENTON, L., WESTON, J., ZUPANCIC, J., STEWART, D. E. & KISS, A. 2009. Effect of peer support on prevention of postnatal depression among high risk women: multisite randomised controlled trial. *British Medical Journal,* 338**,** a3064.
DEPARTMENT FOR COMMUNITIES AND LOCAL GOVERNMENT. 2015. *English indices of deprivation 2015* [Online]. Available: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 [Accessed 30/03/2017].
DEPARTMENT OF HEALTH 2009. *Living well with dementia: A national dementia strategy*, Department of Health.

DEPARTMENT OF HEALTH 2012. Using the Commissioning for Quality and Innovation (CQUIN) payment framework Guidance on new national goals for 2012-13. Department of Health.

DERSIMONIAN, R. & LAIRD, N. 1986. Meta-analysis in clinical trials. *Controlled clinical trials,* 7**,** 177-188.

DODGE, H. H., ZHU, J., MATTEK, N. C., BOWMAN, M., YBARRA, O., WILD, K. V., LOEWENSTEIN, D. A. & KAYE, J. A. 2015. Web-enabled conversational interactions as a method to improve cognitive functions: Results of a 6-week randomized controlled trial. *Alzheimer's & Dementia: Translational Research & Clinical Interventions,* 1**,** 1-12.

DUNN, O. J. 1961. Multiple comparisons among means. *Journal of the American statistical association,* 56**,** 52-64.

EKLUND, M., BENGTSSON-TOPS, A. & LINDSTEDT, H. 2007. Construct and discriminant validity and dimensionality of the Interview Schedule for Social Interaction (ISSI) in three psychiatric samples. *Nordic Journal of Psychiatry,* 61**,** 182-188.

ELLIS, G., MANT, J., LANGHORNE, P., DENNIS, M. & WINNER, S. 2010. Stroke liaison workers for stroke patients and carers: an individual patient data meta-analysis. *Cochrane Database of Systematic Reviews,* 5**,** CD005066.

ELM, E. V., ALTMAN, D. G., EGGER, M., POCOCK, S. J., GØTZSCHE, P. C. & VANDENBROUCKE, J. P. 2007. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *British Medical Journal,* 335**,** 806-808.

ELOVAINIO, M., HAKULINEN, C., PULKKI-RÅBACK, L., VIRTANEN, M., JOSEFSSON, K., JOKELA, M., VAHTERA, J. & KIVIMÄKI, M. 2017a. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. *The Lancet Public Health,* 2**,** e260-e266.

ELOVAINIO, M., SOMMERLAD, A., HAKULINEN, C., PULKKI-RÅBACK, L., VIRTANEN, M., KIVIMÄKI, M. & SINGH-MANOUX, A. 2017b. Structural social relations and cognitive ageing trajectories: evidence from the Whitehall II cohort study. *International journal of epidemiology,* 47**,** 701-708.

ENDICOTT, J., SPITZER, R. L., FLEISS, J. L. & COHEN, J. 1976. The Global Assessment Scale: A procedure for measuring overall severity of psychiatric disturbance. *Archives of general psychiatry,* 33**,** 766-771.

FAN, L. Y., SUN, Y., LEE, H. J., YANG, S. C., CHEN, T. F., LIN, K. N., LIN, C. C., WANG, P. N., TANG, L. Y. & CHIU, M. J. 2015. Marital Status, Lifestyle and Dementia: A Nationwide Survey in Taiwan. *PLoS one,* 10**,** e0139154.

FARRAR, S., YI, D., SUTTON, M., CHALKLEY, M., SUSSEX, J. & SCOTT, A. 2009. Has payment by results affected the way that English hospitals provide care? Difference-in-differences analysis. *British Medical Journal,* 339**,** b3047.

FEIGIN, V. L., LAWES, C. M., BENNETT, D. A. & ANDERSON, C. S. 2003. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *The lancet Neurology,* 2**,** 43-53.

FELDMAN, A., RIZZUTO, D., NARASIMHALU, K., DAHL, A., JOHANSSON, A., GREGORIO, M., WIRDEFELDT, K., GATZ, M., FRATIGLIONI, L. & PEDERSEN, N.

2012. Validity of dementia diagnoses in two Swedish health registers. *Alzheimer's & Dementia,* 8**,** 493.

FOLSTEIN, M. F., FOLSTEIN, S. E. & MCHUGH, P. R. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res,* 12**,** 189-98.

FRATIGLIONI, L., WANG, H. X., ERICSSON, K., MAYTAN, M. & WINBLAD, B. 2000. Influence of social network on occurrence of dementia: a community-based longitudinal study. *The Lancet,* 355**,** 1315-9.

FRÖLICH, L., BLUM-DEGEN, D., BERNSTEIN, H.-G., ENGELSBERGER, S., HUMRICH, J., LAUFER, S., MUSCHNER, D., THALHEIMER, A., TÜRK, A. & HOYER, S. 1998. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. *Journal of neural transmission,* 105**,** 423-438.

FRY, A., LITTLEJOHNS, T. J., SUDLOW, C., DOHERTY, N., ADAMSKA, L., SPROSEN, T., COLLINS, R. & ALLEN, N. E. 2017. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *American journal of epidemiology,* 186**,** 1026-1034.

FU, R., GARTLEHNER, G., GRANT, M., SHAMLIYAN, T., SEDRAKYAN, A., WILT, T. J., GRIFFITH, L., OREMUS, M., RAINA, P. & ISMAILA, A. 2011. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *Journal of clinical epidemiology,* 64**,** 1187-1197.

FULLER, T. D. 2010. Relationship Status, Health, and Health Behavior: An Examination of Cohabiters and Commuters. *Sociological Perspectives,* 53**,** 221-246.

GAO, L., GREEN, E., BARNES, L. E., BRAYNE, C., MATTHEWS, F. E., ROBINSON, L. & ARTHUR, A. 2015. Changing non-participation in epidemiological studies of older people: evidence from the Cognitive Function and Ageing Study I and II. *Age and ageing,* 44**,** 867-873.

GAO, S., HENDRIE, H. C., HALL, K. S. & HUI, S. 1998. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Archives of general psychiatry,* 55**,** 809-815.

GARDNER, J. & OSWALD, A. J. 2006. Do divorcing couples become happier by breaking up? *Journal of the Royal Statistical Society: Series A (Statistics in Society),* 169**,** 319-336.

GARRATT, E., BARNES, H. & DIBBEN, C. 2010. Health administrative data: Exploring the potential for academic research. *St. Andrews: Administrative Data Liaison Service*.

GLASS, T. A., DE LEON, C. F. M., BASSUK, S. S. & BERKMAN, L. F. 2006. Social engagement and depressive symptoms in late life: longitudinal findings. *Journal of aging and health,* 18**,** 604-628.

GLUHM, S., GOLDSTEIN, J., LOC, K., COLT, A., VAN LIEW, C. & COREY-BLOOM, J. 2013. Cognitive performance on the mini-mental state examination and the montreal cognitive assessment across the healthy adult lifespan. *Cognitive and behavioral neurology: official journal of the Society for Behavioral and Cognitive Neurology,* 26**,** 1.

GOLD, A. E., DEARY, I. J., MACLEOD, K. M. & FRIER, B. M. 1995. The effect of IQ level on the degree of cognitive deterioration experienced during acute hypoglycemia in normal humans. *Intelligence,* 20**,** 267-290.

GOLDBERG, D. P. 1972. The detection of psychiatric illness by questionnaire. *Maudsley monograph,* 21.

GOLDMAN, N., KORENMAN, S. & WEINSTEIN, R. 1995. Marital status and health among the elderly. *Social science & medicine,* 40**,** 1717-1730.

GOMM, W., VON HOLT, K., THOMÉ, F., BROICH, K., MAIER, W., FINK, A., DOBLHAMMER, G. & HAENISCH, B. 2016. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurology,* 73**,** 410-416.

GREENE, W. H. & HENSHER, D. A. 2003. A latent class model for discrete choice analysis: contrasts with mixed logit. *Transportation Research Part B: Methodological,* 37**,** 681-698.

GUAITA, A., VACCARO, R., DAVIN, A., COLOMBO, M., VITALI, S. F., POLITO, L., ABBONDANZA, S., VALLE, E., FORLONI, G., FERRETTI, V. V. & VILLANI, S. 2015. Influence of socio-demographic features and apolipoprotein E epsilon 4 expression on the prevalence of dementia and cognitive impairment in a population of 70-74-year olds: the InveCe.Ab study. *Archives of Gerontology & Geriatrics,* 60**,** 334-43.

GUNNELL, D., METCALFE, C., WHILE, D., HAWTON, K., HO, D., APPLEBY, L. & KAPUR, N. 2012. Impact of national policy initiatives on fatal and non-fatal self-harm after psychiatric hospital discharge: time series analysis. *The British Journal of Psychiatry,* 201**,** 233-238.

GUREJE, O., OGUNNIYI, A., KOLA, L. & ABIONA, T. 2011. Incidence of and risk factors for dementia in the Ibadan study of aging. *J. Am. Geriatr. Soc,* 59**,** 869-874.

HAKANSON, K., ROVIO, S., HELKALA, E.-L., VILSKA, A.-R., WINBLAD, B., SOININEN, H., NISSINEN, A., MOHAMMED, A. H. & KIVIPELTO, M. 2009. Association between mid-life marital status and cognitive function in later life: Population based cohort study. *British Medical Journal,* 339**,** 1-12.

HALBERSTADT, J., RUFFMAN, T., MURRAY, J., TAUMOEPEAU, M. & RYAN, M. 2011. Emotion perception explains age-related differences in the perception of social gaffes. *Psychol Aging,* 26**,** 133-6.

HARLOW, H. F., DODSWORTH, R. O. & HARLOW, M. K. 1965. Total social isolation in monkeys. *Proceedings of the National Academy of Sciences,* 54**,** 90-97.

HARRISON, J. E., BUXTON, P., HUSAIN, M. & WISE, R. 2000. Short test of semantic and phonological fluency: Normal performance, validity and test-retest reliability. *British Journal of Clinical Psychology,* 39**,** 181-191.

HARTSHORNE, J. K. & GERMINE, L. T. 2015. When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. *Psychological science,* 26**,** 433-443.

HATCH, D. J. 2013. *The Influence of Widowhood and Sociodemographic Moderators on Dementia and Alzheimer's Disease Risk.* Utah State University.

HE, Y., ZHANG, X. & ZHANG, M. 2000. Psychosocial risk factors for Alzheimer's disease. *Hong Kong J Psychiatry,* 10**,** 2-7.

HEALTH AND SOCIAL CARE INFORMATION CENTRE 2017. HES Data Dictionary: Admitted Patient Care. London: NHS Digital.

HEALTH QUALITY ONTARIO 2008. Social isolation in community-dwelling seniors: an evidence-based analysis. *Ont Health Technol Assess Ser,* 8**,** 1-49.
HEIM, A. W. 1967. *AH4 group test of intelligence,* London, National Foundation for Educational Research.
HELMER, C., DAMON, D., LETENNEUR, L., FABRIGOULE, C., BARBERGER-GATEAU, P., LAFONT, S., FUHRER, R., ANTONUCCI, T., COMMENGES, D., ORGOGOZO, J. M. & DARTIGUES, J. F. 1999. Marital status and risk of Alzheimer's disease: A French population- based cohort study. *Neurology,* 53**,** 1953-1958.
HELMINEN, A., HALONEN, P., RANKINEN, T., NISSINEN, A. & RAURAMAA, R. 1995. Validity assessment of a social support index. *Scandinavian journal of social medicine,* 23**,** 66-74.
HEMINGWAY, H. & MARMOT, M. 1999. Psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. *British Medical Journal,* 318**,** 1460-1467.
HENDERSON, S., DUNCAN-JONES, P., BYRNE, D. & SCOTT, R. 1980. Measuring social relationships the interview schedule for social interaction. *Psychological medicine,* 10**,** 723-734.
HERRETT, E., THOMAS, S. L., SCHOONEN, W. M., SMEETH, L. & HALL, A. J. 2010. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *British journal of clinical pharmacology,* 69**,** 4-14.
HESS, K. R. 1995. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. *Statistics in medicine,* 14**,** 1707-1723.
HILL, A. B. 1965. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *Proc R Soc Med,* 58**,** 295-300.
HOFMAN, A., ROCCA, W., BRAYNE, C., BRETELER, M., CLARKE, M., COOPER, B., COPELAND, J., DARTIGUES, J., DROUX, A. D. S. & HAGNELL, O. 1991. The prevalence of dementia in Europe: a collaborative study of 1980–1990 findings. *International journal of epidemiology,* 20**,** 736-748.
HOLMES, C. & MAYHEW, K. 2012. The changing shape of the UK job market and its implications for the bottom half of earners. *London: Resolution Foundation*.
HOLMES, T. H. & RAHE, R. H. 1967. The social readjustment rating scale. *Journal of psychosomatic research,* 11**,** 213-218.
HOLT-LUNSTAD, J., SMITH, T. B., BAKER, M., HARRIS, T. & STEPHENSON, D. 2015. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspectives on Psychological Science,* 10**,** 227-237.
HOLT-LUNSTAD, J., SMITH, T. B. & LAYTON, J. B. 2010. Social relationships and mortality risk: a meta-analytic review. *PLoS medicine,* 7**,** e1000316.
HUISMAN, M., POPPELAARS, J., VAN DER HORST, M., BEEKMAN, A. T., BRUG, J., VAN TILBURG, T. G. & DEEG, D. J. 2011. Cohort profile: the Longitudinal Aging Study Amsterdam. *International journal of epidemiology,* 40**,** 868-76.
HUTCHEON, J. A., CHIOLERO, A. & HANLEY, J. A. 2010. Random measurement error and regression dilution bias. *British Medical Journal,* 340**,** c2289.
INSTITUTE, T. J. B. 2016. *Joanna Briggs Institute Reviewers' Manual: 2016 edition,* Australia, The Joanna Briggs Institute.
ISMAIL, Z., SMITH, E. E., GEDA, Y., SULTZER, D., BRODATY, H., SMITH, G., AGÜERA-ORTIZ, L., SWEET, R., MILLER, D. & LYKETSOS, C. G. 2016. Neuropsychiatric

symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's & Dementia,* 12**,** 195-202.

ISOMAA, B., ALMGREN, P., TUOMI, T., FORSÉN, B., LAHTI, K., NISSÉN, M., TASKINEN, M.-R. & GROOP, L. 2001. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes care,* 24**,** 683-689.

JACK, C. R., JR., KNOPMAN, D. S., JAGUST, W. J., SHAW, L. M., AISEN, P. S., WEINER, M. W., PETERSEN, R. C. & TROJANOWSKI, J. Q. 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *The Lancet Neurology,* 9**,** 119-28.

JANG, Y., MORTIMER, J. A., HALEY, W. E. & GRAVES, A. R. B. 2004. The role of social engagement in life satisfaction: Its significance among older individuals with disease and disability. *Journal of Applied Gerontology,* 23**,** 266-278.

JIN, Y. P., GATZ, M., JOHANSSON, B. & PEDERSEN, N. L. 2004. Sensitivity and specificity of dementia coding in two Swedish disease registries. *Neurology,* 63**,** 739-41.

JOHANSSON, L., GUO, X., HALLSTROM, T., NORTON, M. C., WAERN, M., OSTLING, S., BENGTSSON, C. & SKOOG, I. 2013. Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: A 38-year longitudinal population study. *BMJ Open,* 3**,** e003142.

JORM, A. F. & JOLLEY, D. 1998. The incidence of dementia: A meta-analysis. *Neurology,* 51**,** 728-733.

JOUNG, I., STRONKS, K., VAN DE MHEEN, H. & MACKENBACH, J. 1995. Health behaviours explain part of the differences in self reported health associated with partner/marital status in The Netherlands. *Journal of Epidemiology and Community Health,* 49**,** 482-488.

KANE, R. L., BUTLER, M., FINK, H. A., BRASURE, M., DAVILA, H., DESAI, P., JUTKOWITZ, E., MCCREEDY, E., NELSON, V. A. & MCCARTEN, J. R. 2017. *Interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-type dementia,* Rockville, MD, Agency for Healthcare Research and Quality (US).

KAPUR, N., HUNT, I., WINDFUHR, K., RODWAY, C., WEBB, R., RAHMAN, M., SHAW, J. & APPLEBY, L. 2013. Psychiatric in-patient care and suicide in England, 1997 to 2008: a longitudinal study. *Psychological Medicine,* 43**,** 61-71.

KATZMAN, R., TERRY, R., DETERESA, R., BROWN, T., DAVIES, P., FULD, P., RENBING, X. & PECK, A. 1988. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 23**,** 138-144.

KIELY, D. K., SIMON, S. E., JONES, R. N. & MORRIS, J. N. 2000. The Protective Effect of Social Engagement on Mortality in Long-Term Care. *Journal of the American Geriatrics Society,* 48**,** 1367-1372.

KIVIMÄKI, M., LUUKKONEN, R., BATTY, G. D., FERRIE, J. E., PENTTI, J., NYBERG, S. T., SHIPLEY, M. J., ALFREDSSON, L., FRANSSON, E. I. & GOLDBERG, M. 2018. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer's & Dementia,* 14**,** 601-609.

KIVIPELTO, M., MANGIALASCHE, F. & NGANDU, T. 2018. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nature Reviews Neurology,* 14**,** 653-666.

KIVIPELTO, M., NGANDU, T., FRATIGLIONI, L., VIITANEN, M., KÅREHOLT, I., WINBLAD, B., HELKALA, E.-L., TUOMILEHTO, J., SOININEN, H. & NISSINEN, A. 2005. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Archives of neurology,* 62**,** 1556-1560.

KNOPMAN, D. S., PETERSEN, R. C., ROCCA, W. A., LARSON, E. B. & GANGULI, M. 2011. Passive case-finding for Alzheimer's disease and dementia in two U.S. communities. *Alzheimer's & Dementia,* 7**,** 53-60.

KNOPMAN, D. S. & RYBERG, S. 1989. A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. *Archives of neurology,* 46**,** 141-145.

KRAVDAL, Ø. 2001. The impact of marital status on cancer survival. *Social science & medicine,* 52**,** 357-368.

KUIPER, J. S., ZUIDERSMA, M., OUDE VOSHAAR, R. C., ZUIDEMA, S. U., VAN DEN HEUVEL, E. R., STOLK, R. P. & SMIDT, N. 2015. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Res Rev,* 22**,** 39-57.

KUIPER, J. S., ZUIDERSMA, M., ZUIDEMA, S. U., BURGERHOF, J. G., STOLK, R. P., OUDE VOSHAAR, R. C. & SMIDT, N. 2016. Social relationships and cognitive decline: a systematic review and meta-analysis of longitudinal cohort studies. *International journal of epidemiology,* 45**,** 1169-1206.

LAIRD, N. M. & WARE, J. H. 1982. Random-effects models for longitudinal data. *Biometrics,* 38**,** 963-74.

LAKEY, B. & COHEN, S. 2000. Social support theory and measurement. Social support measurement and intervention: a guide for health and social scientists, 29–52. Oxford: Oxford University Press.

LANDEIRO, F., BARROWS, P., MUSSON, E. N., GRAY, A. M. & LEAL, J. 2017. Reducing social isolation and loneliness in older people: a systematic review protocol. *BMJ open,* 7**,** e013778.

LANGA, K. M., LARSON, E. B., CRIMMINS, E. M., FAUL, J. D., LEVINE, D. A., KABETO, M. U. & WEIR, D. R. 2016. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. *JAMA Internal Medicine,* 177**,** 51-58.

LARSON, E. B. 2018. Prevention of Late-Life Dementia: No Magic Bullet. *Annals of internal medicine,* 168**,** 77-79.

LARSON, E. B., WANG, L., BOWEN, J. D., MCCORMICK, W. C., TERI, L., CRANE, P. & KUKULL, W. 2006. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of internal medicine,* 144**,** 73-81.

LARSSON, S. C., TRAYLOR, M., MALIK, R., DICHGANS, M., BURGESS, S. & MARKUS, H. S. 2017. Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *British Medical Journal,* 359**,** j5375.

LEARY, M. R., HERBST, K. C. & MCCRARY, F. 2003. Finding pleasure in solitary activities: desire for aloneness or disinterest in social contact? *Personality and Individual Differences,* 35**,** 59-68.

LEE, A. T., RICHARDS, M., CHAN, W. C., CHIU, H. F., LEE, R. S. & LAM, L. C. 2018. Association of daily intellectual activities with lower risk of incident dementia among older Chinese adults. *JAMA Psychiatry,* 75**,** 697-703.

LEECASTER, M., TOTH, D. J., PETTEY, W. B., RAINEY, J. J., GAO, H., UZICANIN, A. & SAMORE, M. 2016. Estimates of social contact in a middle school based on self-report and wireless sensor data. *PloS one,* 11**,** e0153690.

LESKO, C. R. & LAU, B. 2017. Bias due to confounders for the exposure-competing risk relationship. *Epidemiology (Cambridge, Mass.),* 28**,** 20.

LITWIN, H. 1997. Support network type and health service utilization. *Research on aging,* 19**,** 274-299.

LIVINGSTON, G., BARBER, J., RAPAPORT, P., KNAPP, M., GRIFFIN, M., ROMEO, R., KING, D., LIVINGSTON, D., LEWIS-HOLMES, E. & MUMMERY, C. 2014. START (STrAtegies for RelaTives) study: a pragmatic randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of a manual-based coping strategy programme in promoting the mental health of carers of people with dementia. *Health Technology Assessment,* 18**,** 1-242.

LIVINGSTON, G., LEAVEY, G., MANELA, M., LIVINGSTON, D., RAIT, G., SAMPSON, E., BAVISHI, S., SHAHRIYARMOLKI, K. & COOPER, C. 2010. Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. *British Medical Journal,* 341**,** c4184.

LIVINGSTON, G., SOMMERLAD, A., ORGETA, V., COSTAFREDA, S. G., HUNTLEY, J., AMES, D., BALLARD, C., BANERJEE, S., BURNS, A. & COHEN-MANSFIELD, J. 2017. Dementia prevention, intervention, and care. *The Lancet,* 390**,** 2673-2734.

LIVINGSTON, J. D. & BOYD, J. E. 2010. Correlates and consequences of internalized stigma for people living with mental illness: A systematic review and meta-analysis. *Social science & medicine,* 71**,** 2150-2161.

LUBBEN, J. E. 1988. Assessing social networks among elderly populations. *Family & Community Health: The Journal of Health Promotion & Maintenance*.

MANN, F., BONE, J. K., LLOYD-EVANS, B., FRERICHS, J., PINFOLD, V., MA, R., WANG, J. & JOHNSON, S. 2017. A life less lonely: the state of the art in interventions to reduce loneliness in people with mental health problems. *Social psychiatry and psychiatric epidemiology,* 52**,** 627-638.

MANZOLI, L., VILLARI, P., PIRONE, G. M. & BOCCIA, A. 2007. Marital status and mortality in the elderly: a systematic review and meta-analysis. *Social science & medicine,* 64**,** 77-94.

MARIONI, R. E., PROUST-LIMA, C., AMIEVA, H., BRAYNE, C., MATTHEWS, F. E., DARTIGUES, J.-F. & JACQMIN-GADDA, H. 2015. Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study. *BMC public health,* 15**,** 1089.

MARMOT, M. & BRUNNER, E. 2005. Cohort Profile: the Whitehall II study. *International journal of epidemiology,* 34**,** 251-6.

MARTIN, L. T., KUBZANSKY, L. D., LEWINN, K. Z., LIPSITT, L. P., SATZ, P. & BUKA, S. L. 2007. Childhood cognitive performance and risk of generalized anxiety disorder. *International Journal of Epidemiology,* 36**,** 769-775.

MATHERS, C. D., STEVENS, G. A., BOERMA, T., WHITE, R. A. & TOBIAS, M. I. 2015. Causes of international increases in older age life expectancy. *The Lancet,* 385**,** 540-548.
MATIC, A., OSMANI, V. & MAYORA-IBARRA, O. 2012. Analysis of social interactions through mobile phones. *Mobile Networks and Applications,* 17**,** 808-819.
MATTHEWS, F., STEPHAN, B., ROBINSON, L., JAGGER, C., BARNES, L. E., ARTHUR, A., BRAYNE, C., COLLABORATION, A. S. C., COMAS-HERRERA, A. & WITTENBERG, R. 2016. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nature communications,* 7**,** 11398.
MATTHEWS, F. E., ARTHUR, A., BARNES, L. E., BOND, J., JAGGER, C., ROBINSON, L. & BRAYNE, C. 2013. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *The Lancet,* 382**,** 1405-1412.
MBIZVO, G. K., BENNETT, K., SIMPSON, C. R., DUNCAN, S. E. & CHIN, R. F. 2018. Accuracy and utility of using administrative healthcare databases to identify people with epilepsy: a protocol for a systematic review and meta-analysis. *BMJ open,* 8**,** e020824.
MCLAREN, E. 2016. Marriages in England and Wales: 2013. London: Office for National Statistics.
MCPHERSON, M., SMITH-LOVIN, L. & BRASHEARS, M. E. 2006. Social isolation in America: Changes in core discussion networks over two decades. *American sociological review,* 71**,** 353-375.
MEDICAL RESEARCH COUNCIL. 2019. *Cohort Directory - Research - Medical Research Council* [Online]. Available: https://mrc.ukri.org/research/facilities-and-resources-for-researchers/cohort-directory/ [Accessed 2019].
MENG, A., NEXØ, M. A. & BORG, V. 2017. The impact of retirement on age related cognitive decline–a systematic review. *BMC geriatrics,* 17**,** 160.
MENG, X. & D'ARCY, C. 2012. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PloS one,* 7**,** e38268.
MILLSAP, R. E. & EVERSON, H. T. 1993. Methodology review: Statistical approaches for assessing measurement bias. *Applied psychological measurement,* 17**,** 297-334.
MITCHELL, P. H., POWELL, L., BLUMENTHAL, J., NORTEN, J., IRONSON, G., PITULA, C. R., FROELICHER, E. S., CZAJKOWSKI, S., YOUNGBLOOD, M. & HUBER, M. 2003. A short social support measure for patients recovering from myocardial infarction: the ENRICHD Social Support Inventory. *Journal of Cardiopulmonary Rehabilitation and Prevention,* 23**,** 398-403.
MOLLER, J., CLUITMANS, P., RASMUSSEN, L., HOUX, P., RASMUSSEN, H., CANET, J., RABBITT, P., JOLLES, J., LARSEN, K. & HANNING, C. 1998. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *The Lancet,* 351**,** 857-861.
MONTINE, T. J., SONNEN, J. A., MONTINE, K. S., CRANE, P. K. & LARSON, E. B. 2012. Adult Changes in Thought study: dementia is an individually varying convergent syndrome with prevalent clinically silent diseases that may be

modified by some commonly used therapeutics. *Current Alzheimer Research,* 9**,** 718-723.

MORRIS, J. A. & GARDNER, M. J. 1988. Statistics in medicine: Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. *British medical journal (Clinical research ed.),* 296**,** 1313.

MOSSONG, J., HENS, N., JIT, M., BEUTELS, P., AURANEN, K., MIKOLAJCZYK, R., MASSARI, M., SALMASO, S., TOMBA, G. S. & WALLINGA, J. 2008. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS medicine,* 5**,** e74.

MUKADAM, N., SOMMERLAD, A., HUNTLEY, J. & LIVINGSTON, G. 2019. Dementia prevention in low and middle income countries: Population Attributable Fraction for potentially modifiable risk factors. *The Lancet Global Health,* (In press).

MUNIZ-TERRERA, G., MATTHEWS, F., DENING, T., HUPPERT, F. A., BRAYNE, C. & GROUP, C. C. 2009. Education and trajectories of cognitive decline over 9 years in very old people: methods and risk analysis. *Age and Ageing,* 38**,** 277-282.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2015. Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset. *NICE Guideline.* National Institute for Health and Care Excellence.

NELSON, H. E. & WILLISON, J. 1991. *National adult reading test (NART)*, Nfer-Nelson Windsor.

NEWENS, A., FORSTER, D. & KAY, D. 1993. Death certification after a diagnosis of presenile dementia. *Journal of Epidemiology & Community Health,* 47**,** 293-297.

NG, T. P., LEONG, T., CHIAM, P. C. & KUA, E.-H. 2010. Ethnic variations in dementia: the contributions of cardiovascular, psychosocial and neuropsychological factors. *Dementia and geriatric cognitive disorders,* 29**,** 131-138.

NHS DIGITAL. 2018. *Recorded Dementia Diagnoses - November 2018* [Online]. England: NHS Digital. Available: https://digital.nhs.uk/data-and-information/publications/statistical/recorded-dementia-diagnoses/november-2018#resources [Accessed].

NHS ENGLAND. 2017. *Dementia diagnosis monthly workbook* [Online]. Available: https://www.england.nhs.uk/mental-health/dementia/monthly-workbook/ [Accessed 30/03/2017].

NORDSTRÖM, P., NORDSTRÖM, A., ERIKSSON, M., WAHLUND, L.-O. & GUSTAFSON, Y. 2013. Risk factors in late adolescence for young-onset dementia in men: a nationwide cohort study. *JAMA Internal Medicine,* 173**,** 1612-1618.

NORTON, M. C., FAUTH, E., CLARK, C. J., HATCH, D., GREENE, D., PFISTER, R., TSCHANZ, J. T. & SMITH, K. R. 2016. Family member deaths across adulthood predict Alzheimer's disease risk: The Cache County Study. *International Journal of Geriatric Psychiatry,* 31**,** 256-63.

NORTON, S., MATTHEWS, F. E., BARNES, D. E., YAFFE, K. & BRAYNE, C. 2014. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *The Lancet Neurology,* 13**,** 788-794.

NOURHASHEMI, F., AMOUYAL-BARKATE, K., GILLETTE-GUYONNET, S., CANTET, C. & VELLAS, B. 2005. Living alone with Alzheimer's disease: Cross-sectional and

longitudinal analysis in the REAL.FR study. *Journal of Nutrition, Health and Aging,* 9**,** 117-120.

OFFICE FOR NATIONAL STATISTICS. 2014. *2011 Census analysis: Do the demographic and socio-economic characteristics of those living alone in England and Wales differ from the general population?* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/datasets/2011censusanalysisdothedemographicandsocioeconomiccharacteristicsofthoselivingaloneinenglandandwalesdifferfromthegeneralpopulation [Accessed 03/01/2019 2019].

OFFICE FOR NATIONAL STATISTICS 2016. *2011 Census aggregate data*, UK Data Service.

OFFICE FOR NATIONAL STATISTICS 2018. National Life Tables, UK: 2015 to 2017.

OHARA, T., HATA, J., YOSHIDA, D., MUKAI, N., NAGATA, M., IWAKI, T., KITAZONO, T., KANBA, S., KIYOHARA, Y. & NINOMIYA, T. 2017. Trends in dementia prevalence, incidence, and survival rate in a Japanese community. *Neurology,* 88**,** 1925-1932.

ORRELL, M., YATES, L., LEUNG, P., KANG, S., HOARE, Z., WHITAKER, C., BURNS, A., KNAPP, M., LEROI, I. & MONIZ-COOK, E. 2017. The impact of individual Cognitive Stimulation Therapy (iCST) on cognition, quality of life, caregiver health, and family relationships in dementia: A randomised controlled trial. *PLoS medicine,* 14**,** e1002269.

OUDSHOORN, C. G. M., BUUREN, S. & RIJCKEVORSEL, J. L. A. 1999. *Flexible multiple imputation by chained equations of the AVO-95 survey*, TNO Prevention and Health Leiden.

PERERA, G., BROADBENT, M., CALLARD, F., CHANG, C.-K., DOWNS, J., DUTTA, R., FERNANDES, A., HAYES, R. D., HENDERSON, M. & JACKSON, R. 2016a. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. *BMJ open,* 6**,** e008721.

PERERA, G., STEWART, R., HIGGINSON, I. J. & SLEEMAN, K. E. 2016b. Reporting of clinically diagnosed dementia on death certificates: retrospective cohort study. *Age and ageing,* 45**,** 668-673.

PERLMAN, D. & PEPLAU, L. A. 1984. Loneliness research: A survey of empirical findings. *In:* PEPLAU, L. A. & GOLDSTON, S. (eds.) *Preventing the harmful consequences of severe and persistent loneliness.* US: U.S. Government Printing Office.

PERNEGER, T. V. 1998. What's wrong with Bonferroni adjustments. *British Medical Journal,* 316**,** 1236-1238.

PETERSEN, R. C., SMITH, G. E., WARING, S. C., IVNIK, R. J., TANGALOS, E. G. & KOKMEN, E. 1999. Mild cognitive impairment: clinical characterization and outcome. *Archives of neurology,* 56**,** 303-308.

PEW RESEARCH CENTRE 2010. The decline of marriage and rise of new families. *In:* CENTRE, P. R. (ed.). Washington DC, USA.

PIANTADOSI, S., BYAR, D. P. & GREEN, S. B. 1988. The ecological fallacy. *American journal of epidemiology,* 127**,** 893-904.

PICKETT, J., BIRD, C., BALLARD, C., BANERJEE, S., BRAYNE, C., COWAN, K., CLARE, L., COMAS-HERRERA, A., CORNER, L. & DALEY, S. 2018. A roadmap to advance dementia research in prevention, diagnosis, intervention, and care by 2025. *International journal of geriatric psychiatry,* 33**,** 900-906.

PIEPER, C., LACROIX, A. Z. & KARASEK, R. A. 1989. The relation of psychosocial dimensions of work with coronary heart disease risk factors: a meta-analysis of five United States data bases. *American Journal of Epidemiology,* 129**,** 483-494.

PINK, J., O'BRIEN, J., ROBINSON, L. & LONGSON, D. 2018. Dementia: assessment, management and support: summary of updated NICE guidance. *British Medical Journal,* 361**,** k2438.

PIPPENGER, M., HOLLOWAY, R. G. & VICKREY, B. G. 2001. Neurologists' use of ICD-9CM codes for dementia. *Neurology,* 56**,** 1206-1209.

PIRKIS, J. E., BURGESS, P. M., KIRK, P. K., DODSON, S., COOMBS, T. J. & WILLIAMSON, M. K. 2005. A review of the psychometric properties of the Health of the Nation Outcome Scales (HoNOS) family of measures. *Health and quality of life outcomes,* 3**,** 76.

PLASSMAN, B. L., LANGA, K. M., FISHER, G. G., HEERINGA, S. G., WEIR, D. R., OFSTEDAL, M. B., BURKE, J. R., HURD, M. D., POTTER, G. G. & RODGERS, W. L. 2007. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology,* 29**,** 125-132.

PLOS MEDICINE EDITORS 2010. Social relationships are key to health, and to health policy. *PLoS medicine,* 7**,** e1000334.

PRINCE, M., FERRI, C. P., ACOSTA, D., ALBANESE, E., ARIZAGA, R., DEWEY, M., GAVRILOVA, S. I., GUERRA, M., HUANG, Y. & JACOB, K. 2007. The protocols for the 10/66 dementia research group population-based research programme. *BMC public health,* 7**,** 165.

PRINCE, M., KNAPP, M., GUERCHET, M., MCCRONE, P., PRINA, M., COMAS-HERRERA, A., WITTENBERG, R., ADELAJA, B., HU, B. & KING, D. 2014. Dementia UK: update. *Alzheimer's Society*.

PRINCE, M., WIMO, A., GUERCHET, M., ALI, G.-C., WU, Y.-T. & PRINA, M. 2015. World Alzheimer Report 2015. The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. London: Alzheimer's Disease International.

PUBLIC HEALTH ENGLAND. 2018. *Dementia: applying All Our Health* [Online]. Available: https://www.gov.uk/government/publications/dementia-applying-all-our-health/dementia-applying-all-our-health [Accessed January 2019].

RAEL, E., STANSFELD, S. A., SHIPLEY, M., HEAD, J., FEENEY, A. & MARMOT, M. 1995. Sickness absence in the Whitehall II study, London: the role of social support and material problems. *Journal of Epidemiology & Community Health,* 49**,** 474-481.

RAHIMI, J. & KOVACS, G. G. 2014. Prevalence of mixed pathologies in the aging brain. *Alzheimer's research & therapy,* 6**,** 82.

RAWLINGS, A. M., SHARRETT, A. R., SCHNEIDER, A. L., CORESH, J., ALBERT, M., COUPER, D., GRISWOLD, M., GOTTESMAN, R. F., WAGENKNECHT, L. E. &

WINDHAM, B. G. 2014. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Annals of internal medicine,* 161**,** 785-793.
REINHARDT, J. P., BOERNER, K. & HOROWITZ, A. 2006. Good to have but not to use: Differential impact of perceived and received support on well-being. *Journal of Social and Personal Relationships,* 23**,** 117-129.
RICHARDS, M. & DEARY, I. J. 2005. A life course approach to cognitive reserve: a model for cognitive aging and development? *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society,* 58**,** 617-622.
RICHARDS, M. & DEARY, I. J. 2014. A life course approach to cognitive capability. *In:* KUH, D., COOPER, R., HARDY, R., RICHARDS, M. & BEN-SCHLOMO, Y. (eds.) *A life course approach to healthy ageing.* Oxford: Oxford University Press.
RICHARDS, M., HARDY, R. & WADSWORTH, M. E. 2003. Does active leisure protect cognition? Evidence from a national birth cohort. *Social science & medicine,* 56**,** 785-792.
RICHARDS, M. & SACKER, A. 2003. Lifetime antecedents of cognitive reserve. *Journal of clinical and experimental neuropsychology,* 25**,** 614-624.
RITCHIE, K., CARRIÈRE, I., RITCHIE, C., BERR, C., ARTERO, S. & ANCELIN, M.-L. 2010. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *British Medical Journal,* 341**,** c3885.
ROBERTS, B. A., FUHRER, R., MARMOT, M. & RICHARDS, M. 2011. Does retirement influence cognitive performance? The Whitehall II Study. *J Epidemiol Community Health,* 65**,** 958-963.
ROEHR, S., PABST, A., LUCK, T. & RIEDEL-HELLER, S. G. 2018. is dementia incidence declining in high-income countries? A systematic review and meta-analysis. *Clinical epidemiology,* 10**,** 1233.
ROSSOR, M. N., FOX, N. C., MUMMERY, C. J., SCHOTT, J. M. & WARREN, J. D. 2010. The diagnosis of young-onset dementia. *The Lancet Neurology,* 9**,** 793-806.
ROTHMAN, S. M. & MATTSON, M. P. 2010. Adverse stress, hippocampal networks, and Alzheimer's disease. *Neuromolecular medicine,* 12**,** 56-70.
RUBIN, D. B. 2004. *Multiple imputation for nonresponse in surveys*, John Wiley & Sons.
RUDOLPH, J. L., ZANIN, N. M., JONES, R. N., MARCANTONIO, E. R., FONG, T. G., YANG, F. M., YAP, L. & INOUYE, S. K. 2010. Hospitalization in community-dwelling persons with Alzheimer's disease: frequency and causes. *Journal of the American Geriatrics Society,* 58**,** 1542-8.
RUSMAULLY, J., DUGRAVOT, A., MOATTI, J.-P., MARMOT, M. G., ELBAZ, A., KIVIMAKI, M., SABIA, S. & SINGH-MANOUX, A. 2017. Contribution of cognitive performance and cognitive decline to associations between socioeconomic factors and dementia: A cohort study. *PLoS medicine,* 14**,** e1002334.
RUSSELL, D., PEPLAU, L. A. & CUTRONA, C. E. 1980. The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. *Journal of personality and social psychology,* 39**,** 472-480.
SABIA, S., DUGRAVOT, A., DARTIGUES, J.-F., ABELL, J., ELBAZ, A., KIVIMÄKI, M. & SINGH-MANOUX, A. 2017. Physical activity, cognitive decline, and risk of

dementia: 28 year follow-up of Whitehall II cohort study. *British Medical Journal,* 357**,** j2709.

SACZYNSKI, J. S., PFEIFER, L. A., MASAKI, K., KORF, E. S., LAURIN, D., WHITE, L. & LAUNER, L. J. 2006. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. *American Journal of Epidemiology,* 163**,** 433-440.

SANTINI, Z. I., KOYANAGI, A., TYROVOLAS, S., MASON, C. & HARO, J. M. 2015. The association between social relationships and depression: a systematic review. *Journal of affective disorders,* 175**,** 53-65.

SATIZABAL, C. L., BEISER, A. S., CHOURAKI, V., CHÊNE, G., DUFOUIL, C. & SESHADRI, S. 2016. Incidence of dementia over three decades in the Framingham Heart Study. *New England Journal of Medicine,* 374**,** 523-532.

SAVVA, G. M. & ARTHUR, A. 2015. Who has undiagnosed dementia? A cross-sectional analysis of participants of the Aging, Demographics and Memory Study. *Age & Ageing,* 44**,** 642-7.

SCARMEAS, N., ALBERT, S., MANLY, J. & STERN, Y. 2006. Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry,* 77**,** 308-316.

SCARMEAS, N. & STERN, Y. 2003. Cognitive reserve and lifestyle. *J. Clin. Exp. Neuropsychol,* 25**,** 625-633.

SCHMIDT, M. I., DUNCAN, B. B., MILL, J. G., LOTUFO, P. A., CHOR, D., BARRETO, S. M., AQUINO, E. M., PASSOS, V. M. A., MATOS, S. M. & MOLINA, M. D. C. B. 2014. Cohort profile: longitudinal study of adult health (ELSA-Brasil). *International journal of epidemiology,* 44**,** 68-75.

SCHOENFELD, D. 1982. Partial residuals for the proportional hazards regression model. *Biometrika,* 69**,** 239-241.

SCHRIJVERS, E. M., VERHAAREN, B. F., KOUDSTAAL, P. J., HOFMAN, A., IKRAM, M. A. & BRETELER, M. M. 2012. Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology,* 78**,** 1456-1463.

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK. 2017. *Search Filters* [Online]. Available: https://www.sign.ac.uk/search-filters.html [Accessed 02/01/2019 2019].

SEAMAN, S. R. & WHITE, I. R. 2013. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res,* 22**,** 278-95.

SEDGWICK, P. 2015. Meta-analyses: what is heterogeneity? *British Medical Journal,* 350**,** h1435.

SEIDLER, A., BERNHARDT, T., NIENHAUS, A. & FROLICH, L. 2003. Association between the psychosocial network and dementia- a case-control study. *Journal of Psychiatric Research,* 37**,** 89-98.

SHANAS, E. 1979. The family as a social support system in old age. *The gerontologist,* 19**,** 169-174.

SHAPIRO, A. M., BENEDICT, R. H., SCHRETLEN, D. & BRANDT, J. 1999. Construct and concurrent validity of the Hopkins Verbal Learning Test–revised. *The Clinical Neuropsychologist,* 13**,** 348-358.

SHRIER, I. & PLATT, R. W. 2008. Reducing bias through directed acyclic graphs. *BMC medical research methodology,* 8**,** 70.

SINGH-MANOUX, A., DUGRAVOT, A., FOURNIER, A., ABELL, J., EBMEIER, K., KIVIMÄKI, M. & SABIA, S. 2017. Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. *JAMA Psychiatry,* 74**,** 712-718.

SINGH-MANOUX, A., KIVIMAKI, M., GLYMOUR, M. M., ELBAZ, A., BERR, C., EBMEIER, K. P., FERRIE, J. E. & DUGRAVOT, A. 2012. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *British Medical Journal,* 344**,** d7622.

SINGH-MANOUX, A., MARMOT, M. G., GLYMOUR, M., SABIA, S., KIVIMÄKI, M. & DUGRAVOT, A. 2011. Does cognitive reserve shape cognitive decline? *Annals of neurology,* 70**,** 296-304.

SINGLETON, D., MUKADAM, N., LIVINGSTON, G. & SOMMERLAD, A. 2017. How people with dementia and carers understand and react to social functioning changes in mild dementia: qualitative study. *BMJ Open,* 7**,** e016740.

SLATER, P. E. 1963. On social regression. *American Sociological Review***,** 339-364.

SMELSER, N. J. & BALTES, P. B. 2001. *International encyclopedia of the social & behavioral sciences*, Elsevier Amsterdam.

SNOWDON, D. A., KEMPER, S. J., MORTIMER, J. A., GREINER, L. H., WEKSTEIN, D. R. & MARKESBERY, W. R. 1996. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life: Findings from the Nun Study. *JAMA: Journal of the American Medical Association,* 275**,** 528-532.

SOLDAN, A., PETTIGREW, C., CAI, Q., WANG, J., WANG, M.-C., MOGHEKAR, A., MILLER, M. I., ALBERT, M. & TEAM, B. R. 2017. Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. *Neurobiology of aging,* 60**,** 164-172.

SOLOMON, A., NGANDU, T., SOININEN, H., HALLIKAINEN, M. M., KIVIPELTO, M. & LAATIKAINEN, T. 2014. Validity of dementia and Alzheimer's disease diagnoses in Finnish national registers. *Alzheimer's & Dementia,* 10**,** 303-309.

SOMMERLAD, A., PERERA, G., MUELLER, C., SINGH-MANOUX, A., LEWIS, G., STEWART, R. & LIVINGSTON, G. 2019. Hospitalisation of people with dementia: evidence from English electronic health records from 2008 to 2016. *European Journal of Epidemiology,* https://doi.org/10.1007/s10654-019-00481-x.

SOMMERLAD, A., PERERA, G., SINGH-MANOUX, A., LEWIS, G., STEWART, R. & LIVINGSTON, G. 2018a. Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008–2016. *Alzheimer's & Dementia,* 14**,** 933-943.

SOMMERLAD, A., RUEGGER, J., SINGH-MANOUX, A., LEWIS, G. & LIVINGSTON, G. 2018b. Marriage and risk of dementia: systematic review and meta-analysis of observational studies. *J Neurol Neurosurg Psychiatry,* 89**,** 231-238.

SOMMERLAD, A., SINGLETON, D., JONES, R., BANERJEE, S. & LIVINGSTON, G. 2017. Development of an instrument to assess social functioning in dementia: The Social Functioning in Dementia scale (SF-DEM). *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring,* 7**,** 88-98.

SOTO, M., ANDRIEU, S., GARES, V., CESARI, M., GILLETTE-GUYONNET, S., CANTET, C., VELLAS, B. & NOURHASHÉMI, F. 2015. Living alone with Alzheimer's disease and the risk of adverse outcomes: results from the plan de soin et d'aide

dans la maladie d'Alzheimer study. *Journal of the American Geriatrics Society,* 63**,** 651-658.
SPECTOR, A., THORGRIMSEN, L., WOODS, B., ROYAN, L., DAVIES, S., BUTTERWORTH, M. & ORRELL, M. 2003. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. *The British Journal of Psychiatry,* 183**,** 248-254.
SPIJKER, A., VERNOOIJ-DASSEN, M., VASSE, E., ADANG, E., WOLLERSHEIM, H., GROL, R. & VERHEY, F. 2008. Effectiveness of nonpharmacological interventions in delaying the institutionalization of patients with dementia: a meta-analysis. *Journal of the American Geriatrics Society,* 56**,** 1116-1128.
STAFFORD, M., GARDNER, M., KUMARI, M., KUH, D. & BEN-SHLOMO, Y. 2013. Social isolation and diurnal cortisol patterns in an ageing cohort. *Psychoneuroendocrinology,* 38**,** 2737-2745.
STANSFELD, S. & MARMOT, M. 1992. Deriving a survey measure of social support: the reliability and validity of the Close Persons Questionnaire. *Social science & medicine,* 35**,** 1027-1035.
STEPTOE, A., BREEZE, E., BANKS, J. & NAZROO, J. 2012. Cohort profile: the English longitudinal study of ageing. *International journal of epidemiology,* 42**,** 1640-1648.
STERN, Y. 2012. Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology,* 11**,** 1006-1012.
STERNE, J. A., EGGER, M. & SMITH, G. D. 2001. Investigating and dealing with publication and other biases in meta-analysis. *British Medical Journal,* 323**,** 101.
STRINGHINI, S., BERKMAN, L., DUGRAVOT, A., FERRIE, J. E., MARMOT, M., KIVIMAKI, M. & SINGH-MANOUX, A. 2012. Socioeconomic status, structural and functional measures of social support, and mortality: The British Whitehall II Cohort Study, 1985-2009. *American Journal of Epidemiology,* 175**,** 1275-83.
STROUP, D. F., BERLIN, J. A., MORTON, S. C., OLKIN, I., WILLIAMSON, G. D., RENNIE, D., MOHER, D., BECKER, B. J., SIPE, T. A. & THACKER, S. B. 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA: Journal of the American Medical Association,* 283**,** 2008-2012.
SUNDSTRÖM, A., WESTERLUND, O. & KOTYRLO, E. 2016. Marital status and risk of dementia: A nationwide population-based prospective study from Sweden. *BMJ Open,* 6 (1) (no pagination).
SUNDSTRÖM, A., WESTERLUND, O., MOUSAVI-NASAB, H., ADOLFSSON, R. & NILSSON, L.-G. 2014. The relationship between marital and parental status and the risk of dementia. *International Psychogeriatrics,* 26**,** 749-757.
SZRETER, S. R. 1984. The genesis of the Registrar-General's social classification of occupations. *British journal of sociology***,** 522-546.
TARAGANO, F. E., ALLEGRI, R. F., KRUPITZKI, H., SARASOLA, D., SERRANO, C. M., LOÑ, L. & LYKETSOS, C. G. 2009. Mild behavioral impairment and risk of dementia. *The Journal of clinical psychiatry,* 70**,** 584.
TEXTOR, J., VAN DER ZANDER, B., GILTHORPE, M. S., LIŚKIEWICZ, M. & ELLISON, G. T. 2016. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *International journal of epidemiology,* 45**,** 1887-1894.

THE GUARDIAN. 2017. *The battle against loneliness among older people* [Online]. Available: https://www.theguardian.com/healthcare-network/2017/may/10/loneliness-older-people [Accessed 02/01/2019 2019].
THOMPSON, R. A. 1973. A Theory of Instrumental Social Networks. *Journal of Anthropological Research,* 29**,** 244-265.
THOMPSON, S. G. & HIGGINS, J. 2002. How should meta-regression analyses be undertaken and interpreted? *Statistics in medicine,* 21**,** 1559-1573.
TUCKER-DROB, E. M., JOHNSON, K. E. & JONES, R. N. 2009. The cognitive reserve hypothesis: a longitudinal examination of age-associated declines in reasoning and processing speed. *Developmental psychology,* 45**,** 431.
TURKSTRA, L. S. 2008. Conversation-based assessment of social cognition in adults with traumatic brain injury. *Brain Injury,* 22**,** 397-409.
VALCOUR, V. G., MASAKI, K. H., CURB, J. D. & BLANCHETTE, P. L. 2000. The detection of dementia in the primary care setting. *Archives of Internal Medicine,* 160**,** 2964-2968.
VALENZUELA, M., BRAYNE, C., SACHDEV, P., WILCOCK, G. & MATTHEWS, F. 2011. Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort. *American Journal of Epidemiology,* 173**,** 1004-1012.
VALENZUELA, M. J. & SACHDEV, P. 2006. Brain reserve and dementia: a systematic review. *Psychological medicine,* 36**,** 441-454.
VALTORTA, N. K., KANAAN, M., GILBODY, S. & HANRATTY, B. 2016. Loneliness, social isolation and social relationships: what are we measuring? A novel framework for classifying and comparing tools. *BMJ open,* 6**,** e010799.
VAN DER LINDE, R. M., DENING, T., STEPHAN, B. C., PRINA, A. M., EVANS, E. & BRAYNE, C. 2016. Longitudinal course of behavioural and psychological symptoms of dementia: systematic review. *The British Journal of Psychiatry,* 209**,** 366-377.
VAN TILBURG, T. 1995. Delineation of the social network and differences in network size. *In:* DYKSTRA, P. (ed.) *Living Arrangements and social networks of older adults.* Amsterdam: VU University Press.
WADSWORTH, M., KUH, D., RICHARDS, M. & HARDY, R. 2005. Cohort profile: the 1946 national birth cohort (MRC National Survey of Health and Development). *International journal of epidemiology,* 35**,** 49-54.
WARD, G., PERERA, G. & STEWART, R. 2015. Predictors of mortality for people aged over 65 years receiving mental health care for delirium in a South London Mental Health Trust, UK: a retrospective survival analysis. *International journal of geriatric psychiatry,* 30**,** 639-646.
WASSERMAN, S. & FAUST, K. 1997. Social network data. *In:* WASSERMAN, S. (ed.) *Social network analysis: Methods and applications.* Cambridge: Cambridge University Press.
WATTS, D. J., DODDS, P. S. & NEWMAN, M. E. 2002. Identity and search in social networks. *science,* 296**,** 1302-1305.
WEI, J., HU, Y., ZHANG, L., HAO, Q., YANG, R., LU, H., ZHANG, X. & CHANDRASEKAR, E. K. 2017. Hearing Impairment, Mild Cognitive Impairment, and Dementia:

A Meta-Analysis of Cohort Studies. *Dementia and geriatric cognitive disorders extra,* 7**,** 440-452.

WELLS, G., SHEA, B., O'CONNELL, D., PETERSON, J., WELCH, V., LOSOS, M. & TUGWELL, P. 2000. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses* [Online]. Ottawa, Canada: Ottawa Hospital Research Institute, . Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 30/01/2019 2019].

WENGER, G. C. 1991. A network typology: From theory to practice. *Journal of Aging Studies,* 5**,** 147-162.

WEUVE, J., PROUST-LIMA, C., POWER, M. C., GROSS, A. L., HOFER, S. M., THIÉBAUT, R., CHÊNE, G., GLYMOUR, M. M., DUFOUIL, C. & INITIATIVE, M. 2015. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimer's & Dementia,* 11**,** 1098-1109.

WHITLEY, E., DEARY, I. J., DER, G., BATTY, G. D. & BENZEVAL, M. 2012. Paternal age in relation to offspring intelligence in the West of Scotland Twenty-07 prospective cohort study. *PloS one,* 7**,** e52112.

WHITMER, R. A., SIDNEY, S., SELBY, J., JOHNSTON, S. C. & YAFFE, K. 2005. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology,* 64**,** 277-281.

WILKINS, C. H., WILKINS, K. L., MEISEL, M., DEPKE, M., WILLIAMS, J. & EDWARDS, D. F. 2007. Dementia undiagnosed in poor older adults with functional impairment. *Journal of the American Geriatrics Society,* 55**,** 1771-6.

WILKINSON, L. S., KILLCROSS, S. S., HUMBY, T., HALL, F. S., GEYER, M. A. & ROBBINS, T. W. 1994. Social isolation in the rat produces developmentally specific deficits in prepulse inhibition of the acoustic startle response without disrupting latent inhibition. *Neuropsychopharmacology,* 10**,** 61.

WILKINSON, T., LY, A., SCHNIER, C., RANNIKMAE, K., BUSH, K., BRAYNE, C., QUINN, T. J. & SUDLOW, C. L. M. 2018. Identifying dementia cases with routinely collected health data: A systematic review. *Alzheimer's & Dementia*.

WILLIS, S. L. & SCHAIE, K. W. 1999. Intellectual functioning in midlife. *Life in the middle.* Elsevier.

WORLD HEALTH ORGANISATION 2004. *The International statistical classification of diseases and health related problems (ICD-10),* Geneva, World Health Organization.

WU, Y.-T., BEISER, A. S., BRETELER, M. M., FRATIGLIONI, L., HELMER, C., HENDRIE, H. C., HONDA, H., IKRAM, M. A., LANGA, K. M. & LOBO, A. 2017. The changing prevalence and incidence of dementia over time—current evidence. *Nature Reviews Neurology,* 13**,** 327.

XUE, B., CADAR, D., FLEISCHMANN, M., STANSFELD, S., CARR, E., KIVIMÄKI, M., MCMUNN, A. & HEAD, J. 2018. Effect of retirement on cognitive function: the Whitehall II cohort study. *European journal of epidemiology,* 33**,** 989-1001.

YOKOI, T. & OKAMURA, H. 2013. Why do dementia patients become unable to lead a daily life with decreasing cognitive function? *Dementia (London),* 12**,** 551-68.

YOUNG, S. N. 2008. The neurobiology of human social behaviour: an important but neglected topic. *Journal of psychiatry & neuroscience,* 33**,** 391.

ZAVALETA, D., SAMUEL, K. & MILLS, C. 2014. Social isolation: A conceptual and measurement proposal. *OPHI Working Papers 67.*

ZHANG, Z. X., ZAHNER, G. E., ROMAN, G. C., LIU, X. H., WU, C. B., HONG, Z., HONG, X., TANG, M. N., ZHOU, B., QU, Q. M., ZHANG, X. J. & LI, H. 2006. Socio-demographic variation of dementia subtypes in china: Methodology and results of a prevalence study in Beijing, Chengdu, Shanghai, and Xian. *Neuroepidemiology,* 27**,** 177-87.

ZHOU, Z., WANG, P. & FANG, Y. 2018. Social Engagement and Its Change are Associated with Dementia Risk among Chinese Older Adults: A Longitudinal Study. *Scientific reports,* 8**,** 1551.

Appendices

Appendix 1: Systematic review and meta-analysis of marriage and risk of dementia

Cognition

OPEN ACCESS

RESEARCH PAPER

Marriage and risk of dementia: systematic review and meta-analysis of observational studies

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ABSTRACT

Background Being married is associated with healthier lifestyle behaviours and lower mortality and may reduce risk for dementia due to life-course factors. We conducted a systematic review and meta-analysis of studies of the association between marital status and the risk of developing dementia.

Methods We searched medical databases and contacted experts in the field for relevant studies reporting the relationship, adjusted for age and sex, between marital status and dementia. We rated methodological quality and conducted random-effects meta-analyses to summarise relative risks of being widowed, divorced or lifelong single, compared with being married. Secondary stratified analyses with meta-regression examined the impact of clinical and social context and study methodology on findings.

Results We included 15 studies with 812 047 participants. Compared with those who are married, lifelong single (relative risk=1.42 (95% CI 1.07 to 1.90)) and widowed (1.20 (1.02 to 1.41)) people have elevated risk of dementia. We did not find an association in divorced people. Further analyses showed that less education partially confounds the risk in widowhood and worse physical health the elevated risk in lifelong single people. Compared with studies that used clinical registers for ascertaining dementia diagnoses, those which clinically examined all participants found higher risk for being unmarried.

Conclusions Being married is associated with reduced risk of dementia than widowed and lifelong single people, who are also underdiagnosed in routine clinical practice. Dementia prevention in unmarried people should focus on education and physical health and should consider the possible effect of social engagement as a modifiable risk factor.

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INTRODUCTION

The rising number of people living with dementia[1] makes it the current global public health priority,[2] and there is a pressing need to identify modifiable risk factors. Although there are more people with dementia overall, there has been a small decline in the age-specific incidence of dementia in many developed countries[3 4] over the past two decades suggesting that differential lifetime exposure to risk factors in successive generations affects their dementia risk.[4]

Marital status has potential to affect dementia risk by increasing daily social interaction. This may improve cognitive reserve, meaning that an individual has a greater ability to cope with neuropathological damage by using compensatory cognitive approaches from a physically more resilient brain to maintain cognitive ability and daily function.[5] Marriage may result in more frequent social contact, which is associated with reduced dementia risk,[6] and reduced harmful lifestyle behaviours.[7 8] Bereavement or divorce in people who had been married may promote dementia development through stress, which is pathogenic[9] and associated with increased dementia risk.[10] Being unmarried is associated with adverse health behaviours[7] and a range of poorer health outcomes. A meta-analysis of observational studies found lower mortality for married than unmarried people[11]; health of unmarried Americans is worse than that of married people[8]; being married is related to improved cancer survival[12]; and widowhood is associated with disability in older people.[13]

In this study, we aim to synthesise evidence from published studies examining the effect of marital status (married/cohabiting, widowed, divorced/separated and lifelong single) on dementia incidence and the extent to which this risk is modified by sociodemographic factors, study design and methodological quality of the study. We hypothesise that married people are at lower risk of developing dementia compared with unmarried people and that previously married people are at lower risk than those who have been lifelong single.

METHODS

Search strategy

We searched Embase, MEDLINE and PsycInfo databases from their inception to 5 December 2016. Our search terms (online supplementary table 1) identified papers whose titles, abstracts or keywords included terms encompassing marital status and dementia, and we used the Scottish Intercollegiate Guidelines Network filters for observational studies (http://www.sign.ac.uk/methodology/filters.html). We searched references of included studies and systematic reviews and contacted two experts in this field aiming to identify additional studies.

Inclusion criteria

A study was included if:

- it used a prospective or retrospective cohort, case–control or cross-sectional study design
- it reported quantitative data measuring the relationship between dementia and marital status or partner/spouse presence

- it presented results of analyses that were adjusted for age and sex; we contacted authors of studies who reported unadjusted results and included new adjusted data if provided
- marital status was measured and reported separately from other aspects of social network, for example, contact with other family
- the sample consisted of at least 50% of individuals aged 65 years or over at time of dementia ascertainment, or if a younger population was sampled, a study was included if it presented stratified results for an over-65 population
- the sample was derived from a general community-dwelling population. For cohort studies, participants had to be screened for dementia at baseline and prevalent dementia cases excluded.
- it was a published research paper or dissertation; when we found relevant conference abstracts, we contacted the author for details of any eligible published research
- it was published in English.

When two studies reported different analyses of cohort studies, so to avoid duplication, we used only the analysis that had a longer follow-up duration.

Data extraction

One researcher (AS) screened the abstracts of all studies to identify those potentially meeting the inclusion criteria and reviewed full-text articles to confirm eligibility. A second researcher (JR) reviewed a random sample of 10% of the studies to assess agreement and reviewed all included studies to approve eligibility. We used a standardised form (online supplementary table 2) to extract data for evidence synthesis. Extracted information included results and information for the assessment of the risk of bias.

In the one study[14] that used lifelong single people as the reference group, we inverted the ORs, and for this study and another,[15] we calculated CIs based on raw published data.[16] Where marital status categories had been combined (eg, divorced and single people) or results for dementia subtypes rather than all-cause dementia presented, we requested additional data from study authors. We have included new data for three papers.[17–19]

We registered the study protocol prospectively in the PROSPERO register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043161).

Quality rating

We rated methodological quality of included studies using an adapted version of the *Newcastle-Ottawa Criteria*[20] for cohort and case–control studies and the *Joanna Briggs Institute's Checklist*[21] for cross-sectional studies. Full details are in online supplementary tables 3a–c but, in summary, these tools rated the quality of selection, measurement and comparability for all studies and gave a score for cohort and case–control studies (maximum of 9) and cross-sectional studies (maximum 6). Two researchers (AS and JR) assessed the quality of all included studies and discussed discrepancies until consensus was reached.

Statistical analysis

We provide a narrative synthesis of findings from included studies and have pooled results where studies have used the same measurements, calculating random-effects estimates using STATA V.14. The random-effects model allows for HRs and ORs to be incorporated into the same meta-analysis[22] and accounts for heterogeneity between studies.[23] All included studies provided an estimate of relative risk and CI that we used for the analysis. We measured heterogeneity between the studies using the χ^2 test and the I^2 statistic and considered, a priori, that I^2 >50% indicated substantial heterogeneity. Where studies provided estimates of relative risk from different multivariate models, we included the result from the model with the largest number of covariates.

Our main analyses compared risk of all-cause dementia in married people to those who were widowed, divorced or lifelong single for studies that ascertained dementia diagnosis status from clinical assessment. We conducted prespecified secondary analyses. We analysed the association between marital status and risk of Alzheimer's or vascular dementia. We conducted stratified analyses and used meta-regression[24] to quantify the effect of various study design factors on the association between marital status and all-cause mortality: (1) dementia case ascertainment method: clinical assessment of study participants versus clinical register data; (2) study type: cohort versus other studies; (3) study quality rating; and (4) time period of study conduct, based on mean year of birth of study participants.

We assessed the effect of confounder adjustment on the relative risk using stratified analyses of studies that adjusted only for age and sex versus studies that additionally adjusted for education or baseline cognition versus studies that additionally adjusted for physical health. We assessed for evidence of publication bias using funnel plots and Egger's weighted regression method.[25]

RESULTS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) diagram (figure 1) shows our search results and reasons for study exclusion. Sixteen studies fulfilled our inclusion criteria, but we excluded one publication[26] from our meta-analysis as it reported data from the same cohort as another study[27] but with shorter follow-up. The 15 studies in our analyses included 812 047 people, of whom 29 610 had any form of dementia. Of these, 61 012 had a clinical assessment for dementia and 751 035 had dementia status ascertained from clinical records.

Table 1 describes key study characteristics. Nine were cohort studies,[17–19 27–32] two case–control[14 15] and four cross-sectional.[33–36] Eight included studies were set in European countries, four in Asia, two from USA and one from Brazil. The mean year of birth of study participants ranged from 1897 to 1939. Studies typically measured marital status at study inception (mean age 72.8 (SD 7.2) years.) In the cohort studies, the duration of follow-up before dementia assessment was 3 to 20.9 (mean 8.5, SD 5.5) years.

Married people accounted for between 27.8% and 80.1% of the sample (widowed=7.8% to 48.0%, divorced=0%to 16%, lifelong single=0% to 32.6%). Two studies[34 36] combined divorced and lifelong single people (6.1% and 10.1%). The mean methodological quality score for the cohort studies was 5.4/9, 2/9 for case–control studies and 3.8/6 for cross-sectional studies. Full details of methodological assessment are in online supplementary tables 3a–c. All included cohort studies analysed complete cases, excluding participants who had withdrawn from study.

Marital status was, in all but two of the cohort studies[30 32] which used registry data, reported by the participant or a close informant. No studies provided further details about this assessment nor was there any information on duration of exposure to a particular marital status category. In one cohort study,[32] marital status was ascertained from a Swedish central population register, and in another cohort,[30] a marriage registry was used to confirm marital status. For the two case–control studies, those with dementia (or, if incapable of answering, an informant) were asked about their

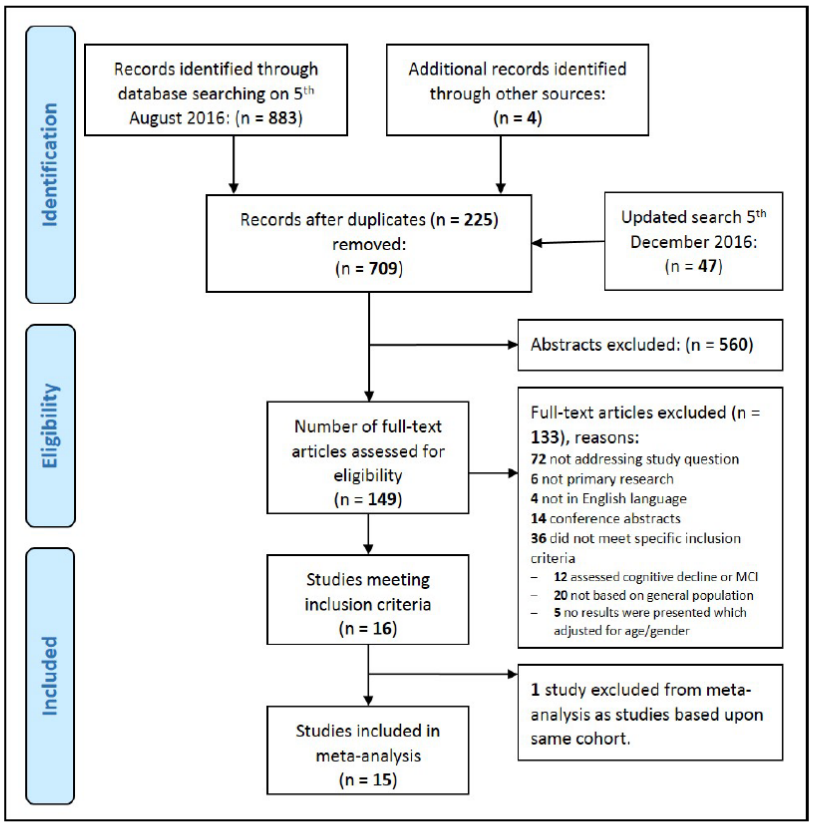

Figure 1 PRISMA diagram of study identification and selection. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis. MCI, Mild cognitive impairment.

marital status at age 30 and 50 years and 10 years prior to interview[14] or at time of diagnosis.[15]

All but three of the studies clinically examined all participants for ascertaining diagnostic status (outcome). The other studies[14 15 32] ascertained diagnostic status from routine clinical registers and, for one of these studies,[32] death registers. Except for the cohort study[32] that exclusively used register data, none reported whether they ascertained dementia status from death registers. The clinical examination used in the majority of studies was a staged approach: a screening phase followed by a more detailed neuropsychological and functional assessment and an expert consensus panel to establish diagnostic status.

Main meta-analysis: widowed, divorced or lifelong single versus married people and risk of all-cause dementia

We pooled risk estimates from studies that evaluated the risk of all-cause dementia according to marital status category, with dementia case ascertainment based on clinical examination (figure 2). Nine studies analysed the risk of all-cause dementia in widowed versus married people and we found that in widowed, compared with married, people, the relative risk of dementia=1.20 (95% CI 1.02 to 1.41). The relative risk for divorced versus married people from seven studies=0.99 (0.71 to 1.37) and for the six studies that analysed dementia risk for lifelong single people, RR=1.42 (1.07 to 1.90).

Secondary analyses

Widowed, divorced or lifelong single versus married people and risk of Alzheimer's disease and vascular dementia

Fewer studies examined the risk of dementia subtypes according to marital status. Eight[14 15 17 27 29 30 35 36] examined the risk of Alzheimer's disease (1891 cases) in widowed versus married people and found a pooled relative risk of 1.24 (0.97 to 1.60). The risk of Alzheimer's disease in five[14 15 27 30 35] studies of divorced (0.89 (0.58 to 1.36)) and three[15 27 35] of lifelong single (1.07 (0.75 to 1.52)) people was not different to that of married people. For vascular dementia (372 cases), no effect of marital status on dementia risk was found in pooled estimates from the three studies[14 35 36] that examined the risk for widowed versus married people (pooled RR=0.90 (0.40 to 2.04)) or the two[14 35] studies that examined risk in lifelong single people versus married (2.66 (0.85 to 8.28)). Only one study[14] compared the risk of vascular dementia in divorced and married people and found no difference.

Widowed, divorced or lifelong single versus married people and risk of all-cause dementia stratified by sex

Two studies (online supplementary table 2) analysed the relationship between marital status and dementia separately for men and women. For one study,[32] the outcome was all-cause dementia, and for the other,[15] it was Alzheimer's disease

Table 1 Characteristics of included studies

Study (first author and year of publication)	Study design	Country	Number of participants	Mean year of birth	Mean age at marital status evaluation (years)	Baseline marital status of participants (%)				Mean/range of follow-up (years)	Method of dementia case ascertainment	Quality rating
						Married	Widowed	Divorced	Lifelong single			
Amieva 2010[27]	Cohort	France	2089	1914	74	60.7	32.5	2.7	4.2	5–15	Clinical assessment	5
Arai 2004[28]	Cohort	Japan	853	1929	69	71	29 (unmarried)			5	Clinical assessment	3
Bae 2014[17]	Cohort	S Korea	359	1936	72	70.2	29.8	0	0	3.5	Clinical assessment	3
Bickel 1994[18]	Cohort	Germany	331	1918	74	42.4	47.5	3.8	6.4	7–8	Clinical assessment	5
Fratiglioni 2000[19]	Cohort	Sweden	1368	1905	82	27.8	45.4	5.9	20.9	3	Clinical assessment	6
Håkansson 2009[29]	Cohort	Sweden	2000	1926	51	80.1	7.8	4.4	7.8	20.9	Clinical assessment	8
Hatch 2013[30]	Cohort	USA	5092	1920	75	65.9	29.9	4.1	N/A	12	Clinical assessment	8
Sundström 2014[31]	Cohort	Sweden	1677	1919	75	57.6	14.2	5.7	32.6	8.6	Clinical assessment	7
Sundström 2016[32]	Cohort	Sweden	750129	1928	69	64.9	8.4	16.0	10.8	6	Clinical register/death register	9
Beard 1992[15]	Case-control	USA	482	1897	80	28.8	48.0	5.4	17.8	N/A	Secondary care clinical register	3
Seidler 2003[14]	Case-control	Germany	424	1924	77	78.5	11.1	3.8	6.6	N/A	General practice clinical register	2
Correa Ribeiro 2013[33]	Cross-sectional	Brazil	683	1931	78	41.6	40.8	7.5	10.1	N/A	Clinical assessment	3
Fan 2015[34]	Cross-sectional	Taiwan	10432	1936	76	64.2	31.0	4.8 (Div/single)		N/A	Clinical assessment	4
Guaita 2015[35]	Cross-sectional	Italy	1321	1939	72	67.1	24.6	2.2	6.1	N/A	Clinical assessment	4
Zhang 2006[36]	Cross-sectional	China	34807	1929	68	77.4	20.8	1.6 (Div/single)		N/A	Clinical assessment	4

N/A,Not applicable

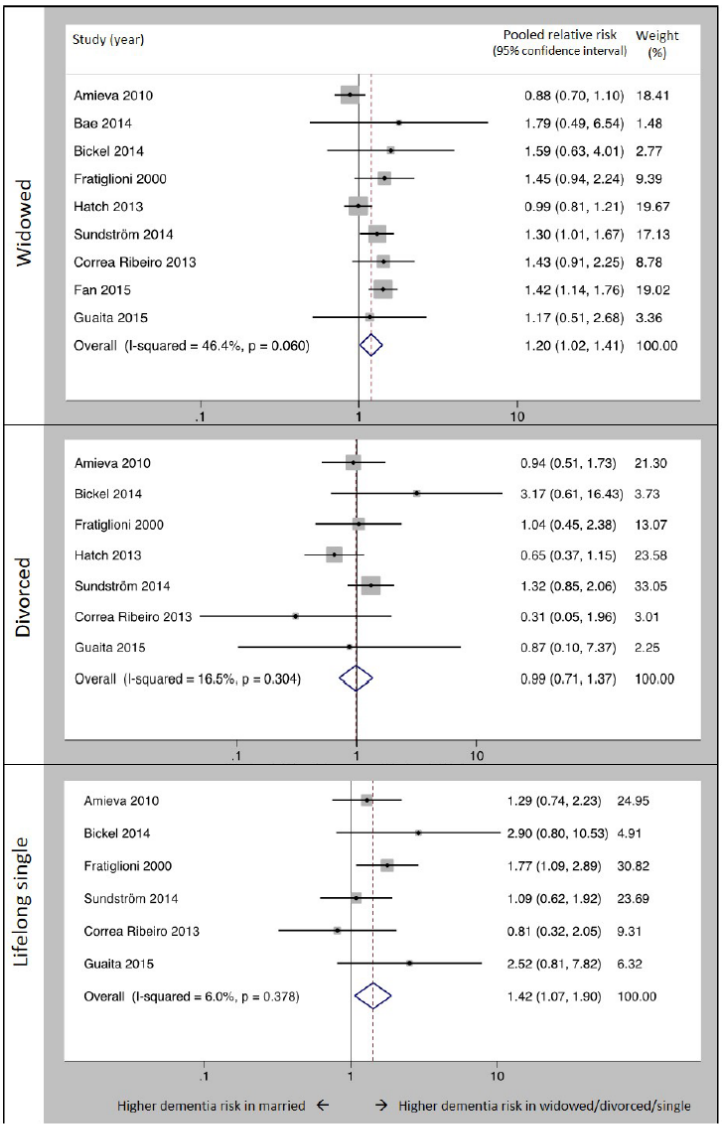

Figure 2 Forest plot showing pooled relative risk of dementia in widowed, divorced and lifelong single people versus married people when dementia was ascertained by clinical examination. Notes: figures are based on random-effects meta-analysis; included studies ascertained dementia diagnostic status using a clinical examination of study participants.

so meta-analysis was not possible. Neither study found any difference between men and women in the association of marital status and dementia.

Impact of study design on association between marital status and all-cause dementia

Widowed, divorced or lifelong single versus married people and risk of all-cause dementia stratified by case ascertainment method

There was evidence that the method of dementia case ascertainment affected the risk estimates (table 2). Studies using clinical examination for dementia ascertainment produced higher pooled estimates for the effect of being widowed (1.20 (1.02 to 1.41) versus 1.12 (1.07 to 1.18)) or lifelong single (1.42 (1.07 to 1.90) versus 1.23 (1.17 to 1.29)), and this difference nearly reached significance for the comparison of single and married people (p=0.06). The risk of dementia for divorced compared with married people was slightly lower but neither risk estimate was significant.

Widowed, divorced or lifelong single versus married people and risk of all-cause dementia stratified by study type

The pooled risk estimate (table 2) for dementia in widowed versus married people was lower (meta-regression: p=0.004) from the seven cohort studies[17–19 27 30–32] (1.10 (1.05 to 1.28))

Table 2 Meta-regression of the risk of all-cause dementia according to marital status, stratified by study time period, case ascertainment methodology, study type and study quality

		Widowed versus married		Divorced versus married		Lifelong single versus married	
		Stratified analysis: Relative risk (95% CI) Number of studies	Meta-regression coefficient (95% CI) p value	Stratified analysis: Relative risk (95% CI) Number of studies	Meta-regression coefficient (95% CI) p-value	Stratified analysis: Relative risk (95% CI) Number of studies	Meta-regression coefficient (95% CI) p value
Method of case ascertainment	Clinical assessment	1.20 (1.02 to 1.41) n=9	b=−0.06 (−0.18 to 0.05) p=0.29	0.99 (0.71 to 1.37) n=7	b=0.34 (0.06 to 0.62) p=0.02	1.42 (1.07 to 1.90) n=6	b=−0.27 (−0.55 to 0.01) p=0.06
	Clinical registers	1.12 (1.07 to 1.18) n=2		1.11 (0.52 to 2.38) n=2		1.23 (1.17 to 1.29) n=2	
Study type	Cohort	1.10 (1.05 to 1.28) n=7	b=0.28 (0.09 to 0.46) p=0.004	1.16 (0.87 to 1.55) n=6	b=−0.83 (−1.69 to 0.03) p=0.06	1.24 (1.17 to 1.30) n=5	b=0.08 (−0.45 to 0.62) p=0.76
	Case–control/cross-sectional	1.39 (1.16 to 1.67) n=4		0.55 (0.23 to 1.31) n=3		1.21 (0.67 to 2.18) n=3	
Global quality score	Higher quality ≥6	1.13 (1.02 to 1.31) n=4	b=0.08 (-0.06 to 0.23) p=0.27	1.16 (0.83 to 1.62) n=4	b=−0.40 (-0.88 to 0.08) p=0.10	1.26 (1.09 to 1.45) n=3	b=0.20 (-0.17 to 0.57) p=0.29
	Lower quality <6	1.22 (0.96 to 1.54) n=7		0.88 (0.54 to 1.44) n=5		1.33 (0.92 to 1.92) n=5	
	Increase in quality by one point	b=−0.04 (−0.08 to −0.002) p=0.04 n=11		b=0.12 (0.01 to 0.24) p=0.04 n=9		b=−0.05 (−0.13 to 0.03) p=0.21 n=8	
Time period	Mean DoB before 1927	1.11 (0.93 to 1.31) n=6	b=0.15 (−0.14 to 0.43) p=0.32	0.98 (0.71 to 1.37) n=6	b=0.35 (0.08 to 0.63) p=0.01	1.40 (1.06 to 1.85) n=5	b=−0.22 (−0.50 to 0.06) p=0.13
	Mean DoB after 1927	1.23 (1.06 to 1.43) n=5		1.08 (0.50 to 2.35) n=3		1.24 (0.94 to 1.62) n=3	
	Mean year of birth 10 years later	b=0.08 (−0.08 to 0.23) p=0.34 n=11		b=0.24 (0.01 to 0.47) p=0.04 n=9		b=−0.15 (−0.33 to 0.02) p=0.09 n=8	

Figures are based on random-effects meta-analysis.
DoB, date of birth.

than the four cross-sectional or case–control studies[14 33 34 36] (1.39 (1.16 to 1.67)) that examined this association. There were no differences between cohort and other studies in pooled estimates of dementia risk in lifelong single versus married people or divorced versus married people.

Widowed, divorced or lifelong single versus married people and risk of all-cause dementia stratified by study quality

Stratified analyses of higher versus lower quality studies and meta-regression analysis of the effect of study quality on risk estimates found no effect of study quality on relative risk for widowed or lifelong single people. The four higher quality studies[19 30–32] produced a slightly increased risk for divorced people than the five lower quality studies[14 18 27 33 35] but in neither strata was divorce related to dementia risk.

Widowed, divorced or lifelong single versus married people and risk of all-cause dementia by time period

Meta-regression analysis suggested that the relative risk of dementia in divorced people increased by 24% (95% CI 1% to 47%) for studies of participants born 10 years later (table 2), although risk remained non-significant when comparing the newer and older studies. There was some evidence that time period modified the effect of being lifelong single on risk of dementia: the risk of dementia in single people was 15% lower (9% CI 33% lower to 2% higher) for every 10 years later that participants were born. In the oldest studies (participants born on average before 1927), the risk of dementia in lifelong single versus married people was 1.40 (1.06 to 1.85) and for the most recent studies (of people born after 1927), the risk was 1.24 (0.94 to 1.62). No significant modifying effect of time period was found for the risk of dementia in widowed people.

Effect of covariate adjustment on risk estimates

For dementia risk in widowed versus married people, the pooled risk estimates (table 3) from the three studies[17 18 31] that adjusted only for age and sex (1.33 (1.05 to 1.69)) was higher than the five studies[14 19 30 33 35] that adjusted additionally for education or baseline cognitive function (1.12 (0.95 to 1.31)). No further attenuation of the effect was found in three studies[27 32 34] that additionally adjusted for physical health (1.12 (0.92 to 1.37)).

For lifelong single people, the risk estimate for dementia was not affected by adjustment for education, but the relative risk of dementia in single versus married people fell from 1.45 (0.97 to 2.19) to 1.23 (1.17 to 1.29) in studies that adjusted for physical health.

Publication bias

In funnel plots (online supplementary figure 1), there was no clear evidence of asymmetry suggesting publication bias. Weighted regression (Egger) test indicated that there was unlikely to be publication bias in studies examining widowed (p=0.30) or lifelong single (p=0.35) people but that there may have been for studies of divorced people (p=0.04).

DISCUSSION

Our study summarised all accessible published evidence and found that people who are lifelong single have a 42% higher risk and that those who are widowed have a 20% higher risk of developing dementia than those who are married in studies adjusted for age and sex. We found no evidence that dementia risk in divorced people differs from married people. The reduced risk in married people persisted in sensitivity analyses, indicating the robustness of the findings. Similar direction and magnitude of effect were found for dementia subtypes, but these

Table 3 Meta-analyses of the risk of all cause dementia according to marital status stratified by covariate adjustment.

	Widowed versus married		Divorced versus married		Lifelong single versus married	
	Relative risk (95% CI) p value	Number of studies Heterogeneity statistic	Relative risk (95% CI) p value	Number of studies Heterogeneity statistic	Relative risk (95% CI) p value	Number of studies Heterogeneity statistic
Studies adjusted for age and sex	1.33 (1.05 to 1.69) p=0.02	n=3 I^2=0%	1.41 (0.90 to 2.21) p=0.14	n=2 I^2=1.5%	1.49 (0.61 to 3.63) p=0.38	n=2 I^2=46.1%
Studies adjusted for age, sex and education	1.12 (0.95 to 1.31) p=0.19	n=5 I^2=0%	0.70 (0.47 to 1.06) p=0.10	n=5 I^2=0%	1.45 (0.97 to 2.19) p=0.005	n=4 I^2=14.6%
Studies adjusted for age, sex, education and physical health	1.12 (0.92 to 1.37) p=0.26	n=3 I^2=77.8%	1.30 (0.93 to 1.81) p=0.12	n=2 I^2=42.5%	1.23 (1.17 to 1.29) p=0.36	n=2 I^2=0%

Figures are based on random-effects meta-analysis.

estimates were non-significant as these analyses had fewer participants. Study design affects estimates of dementia risk. Higher relative risk of dementia for lifelong single and widowed people was found in studies that diagnosed dementia following clinical examination of all participants than in those that ascertained diagnostic status from routinely collected data; and lower risk was found for widowed people in cohort studies than in case–control or cross-sectional studies. There is some indication that the elevated risk in lifelong single people has decreased over time, with more recent studies finding smaller associations. We find that much of the increased risk in widowed people is attenuated after adjustment for education and that confounding by physical health explains part of the increased risk of dementia in lifelong single people.

Our findings may be explained in one or more ways. First, being married may change individuals' exposure to other protective and risk factors throughout their subsequent lifespan; this is supported by our identification of confounding factors affecting this risk and evidence showing married people to be more likely to have a healthy lifestyle. The residual increased risk for lifelong single people in studies that adjusted for age, sex, education and physical health is likely to be due to different social engagement in married and single people,[37] which may contribute to building cognitive reserve and reducing dementia risk[6] over the lifespan. The magnitude of effect of marital status on dementia is higher than the risk for mortality in unmarried compared with married people (RR=1.1),[11] supporting the idea that marriage's effect on dementia risk is more than just improving physical health and that there may a direct cognitive benefit of being married.

Second, the end of marriage through bereavement could act directly to increase dementia risk, through the detrimental effect of stress on hippocampal neurons[9] or cognition,[10] and this theory could explain the increased dementia risk for widowed, but not divorced, people, as studies have found widowhood to be more stressful than divorce.[38 39] Third, developing dementia could be related to other underlying cognitive or personality traits meaning that in societies where marriage was the social norm, people with difficulties in flexibility of thought or communication and consequent smaller lifelong cognitive reserve (therefore more likely to develop dementia) may be less likely to marry. This explanation may be supported by our finding that the risk for lifelong single people is possibly reduced in more recent times. Remaining unmarried has become more common,[40 41] and it may be that single people born in the latter half of the 20thcentury have fewer unusual cognitive and personality characteristics.

Our findings, from large populations, across numerous countries and time periods are the strongest evidence yet that married people are less likely to develop dementia. We searched the literature systematically, sought additional studies where possible by contacting authors to gain additional data where published information was insufficient and followed PRISMA guidance in the conduct and reporting of this study.[42] The main limitations of this review relate to the methodology of included studies. We could not investigate the effect of the duration of being widowed or divorced as the included studies did not report this, and we could only investigate the impact of potential confounders that were measured and analysed in studies, limiting our investigation of potential explanations for our findings. Our findings in relation to divorced people are less robust as there were fewer divorced people in the included studies. While our search terms were thorough, supporting our belief that we identified all studies examining this relationship, we may have missed eligible studies. This is a particular risk for observational studies examining the effect of other exposures on dementia risk, which may have reported marital status as a potential covariate, although less likely for this review as we aimed to only include studies that adjusted the relationship between marital status and dementia for age and sex.

Our finding of a 42% increased risk in lifelong single people compares closely to other known dementia risk factors incorporated in National Institute for Health and Care Excellence guidelines[43] such as physical inactivity (RR=1.4) and less education, hypertension or smoking (RR for each=1.6).[44] Our findings support the need for further work to develop preventative approaches in these lifestyle domains and indicate this may be particularly important for the high-risk groups of widowed and lifelong single people.

We also found that routine clinical registers underestimate the risk of dementia in these groups, which is likely to be because register data has poor sensitivity for detecting dementia[45] and unmarried people are more likely to be undiagnosed in routine practice.[46] Diagnosing dementia in people who attend clinic alone is more difficult, due to lack of collateral information and because individuals with dementia may not complain of memory impairment,[47] so clinicians should have a high index of suspicion for dementia in these groups.

Future research should explore the mechanism of the relationship between marital status and dementia in order to develop interventions. It should, in particular, evaluate the contribution of social contact and health behaviours; use studies with sufficient follow-up to allow exploration of premarriage cognitive characteristics; and use cohort studies with sufficient detail on the duration of marriage, widowhood or divorce to allow the exploration of a dose–response effect.

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Contributors AS, AS-M, GL and GL conceived and designed the study. AS conducted the literature search. AS and JR assessed manuscripts for inclusion in the study and rated them for quality. AS extracted data and performed analyses. All authors contributed substantially to drafting the article and revising it critically for intellectual content and gave final approval to the submitted manuscript.

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REFERENCES

1 Prince M, Wimo A, Guerchet M, *et al*; *World alzheimer report 2015. The global impact of dementia: an analysis of prevalence, incidence, cost and trends*. London: Alzheimer's Disease International, 2015.
2 Prince M, Guerchet M, Prina M. *The global impact of dementia 2013-2050*. London: Alzheimer's Disease International, 2013.
3 Matthews FE, Arthur A, Barnes LE, *et al*. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet* 2013;382:1405–12.
4 Langa KM, Larson EB, Crimmins EM, *et al*. A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Internal Medicine* 2016.
5 Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* 2012;11:1006–12.
6 Kuiper JS, Zuidersma M, Oude Voshaar RC, *et al*. Social relationships and risk of dementia: a systematic review and meta-analysis of longitudinal cohort studies. *Ageing Res Rev* 2015;22:39–57.
7 Joung IM, Stronks K, van de Mheen H, *et al*. Health behaviours explain part of the differences in self reported health associated with partner/marital status in The Netherlands. *J Epidemiol Community Health* 1995;49:482–8.
8 Fuller TD, Tech V. Relationship status, health, and health behavior: an examination of cohabiters and commuters. *Sociological Perspectives* 2010;53:221–45.
9 Rothman SM, Mattson MP. Adverse stress, hippocampal networks, and Alzheimer's disease. *Neuromolecular Med* 2010;12:56–70.
10 Johansson L, Guo X, Hällström T, *et al*. Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 38-year longitudinal population study. *BMJ Open* 2013;3:e003142.
11 Manzoli L, Villari P, M Pirone G, *et al*. Marital status and mortality in the elderly: a systematic review and meta-analysis. *Soc Sci Med* 2007;64:77–94.
12 Kravdal O. The impact of marital status on cancer survival. *Soc Sci Med* 2001;52:357–68.
13 Goldman N, Korenman S, Weinstein R. Marital status and health among the elderly. *Soc Sci Med* 1995;40:1717–30.
14 Seidler A, Bernhardt T, Nienhaus A, *et al*. Association between the psychosocial network and dementia--a case-control study. *J Psychiatr Res* 2003;37:89–98.
15 Beard CM, Kokmen E, Offord KP, *et al*. Lack of association between Alzheimer's disease and education, occupation, marital status, or living arrangement. *Neurology* 1992;42:2063–8.
16 Morris J. In: Gardner MJ, Altman DG, *Calculating confidence intervals for relative risk, odds ratios and standardised ratios and rates. Statistics with Confidence–Confidence Intervals and Statistical Guidelines*. London: BMJ Publishing Group, 1995.
17 Bae JB, Kim YJ, Han JW, *et al*. Incidence of and risk factors for Alzheimer's disease and mild cognitive impairment in Korean elderly. *Dement Geriatr Cogn Disord* 2015;39:105–15.
18 Bickel H, Cooper B. Incidence and relative risk of dementia in an urban elderly population: findings of a prospective field study. *Psychol Med* 1994;24:179–92.
19 Fratiglioni L, Wang HX, Ericsson K, *et al*. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* 2000;355:1315–9.
20 Wells G, Shea B, O'connell D, *et al*; *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*, 2000.
21 Institute TJB. *Joanna briggs institute reviewers' manual: 2016 edition*. Australia: The Joanna Briggs Institute, 2016.
22 Fu R, Gartlehner G, Grant M, *et al*. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol* 2011;64:1187–97.
23 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
24 Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21:1559–73.
25 Sterne JA, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. *British Medical Journal* 2001;323:101.
26 Helmer C, Damon D, Letenneur L, *et al*. Marital status and risk of Alzheimer's disease: a French population-based cohort study. *Neurology* 1999;53:1953–8.
27 Amieva H, Stoykova R, Matharan F, *et al*. What aspects of social network are protective for dementia? Not the quantity but the quality of social interactions is protective up to 15 years later. *Psychosom Med* 2010;72:905–11.
28 Arai A, Katsumata Y, Konno K, *et al*. Sociodemographic factors associated with incidence of dementia among senior citizens of a small town in Japan. *Care Manag J* 2004;5:159–65.
29 Håkansson K, Rovio S, Helkala EL, *et al*. Association between mid-life marital status and cognitive function in later life: population based cohort study. *BMJ* 2009;339:b2462–12.
30 Hatch DJ. *The influence of widowhood and sociodemographic moderators on dementia and alzheimer's disease risk*, 2013.
31 Sundström A, Westerlund O, Mousavi-Nasab H, *et al*. The relationship between marital and parental status and the risk of dementia. *Int Psychogeriatr* 2014;26:749–57.
32 Sundström A, Westerlund O, Kotyrlo E. Marital status and risk of dementia: a nationwide population-based prospective study from Sweden. *BMJ Open* 2016;6:e008565.
33 Correa Ribeiro PC, de Souza Lopes C, Lourenço RA. Prevalence of dementia in elderly clients of a private health care plan: a study of the FIBRA-RJ, Brazil. *Dement Geriatr Cogn Disord* 2013;35:77–86.
34 Fan LY, Sun Y, Lee HJ, *et al*. Marital status, lifestyle and dementia: a nationwide survey in Taiwan. *PLoS One* 2015;10:e0139154.
35 Guaita A, Vaccaro R, Davin A, *et al*. Influence of socio-demographic features and apolipoprotein E epsilon 4 expression on the prevalence of dementia and cognitive impairment in a population of 70-74-year olds: the InveCe.Ab study. *Arch Gerontol Geriatr* 2015;60:334–43.
36 Zhang ZX, Zahner GE, Román GC, *et al*. Socio-demographic variation of dementia subtypes in china: Methodology and results of a prevalence study in Beijing, Chengdu, Shanghai, and Xian. *Neuroepidemiology* 2006;27:177–87.
37 Sarkisian N, Gerstel N. Does singlehood isolate or integrate? Examining the link between marital status and ties to kin, friends, and neighbors. *Journal of Social and Personal Relationships* 2015:0265407515597564.
38 Gardner J, Oswald AJ. Do divorcing couples become happier by breaking up? *J R Stat Soc Ser A Stat Soc* 2006;169:319–36.
39 Holmes TH, Rahe RH. The social readjustment rating scale. *J Psychosom Res* 1967;11:213–8.
40 Pew Research Centre. *The decline of marriage and rise of new families*. Washington DC, USA, 2010.
41 McLaren E. *Marriages in England and Wales: 2013*. London: Office for National Statistics, 2016.
42 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama* 2000;283:2008–12.
43 NICE. *Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset*: National Institute for Health and Clinical Excellence, 2015.
44 Norton S, Matthews FE, Barnes DE, *et al*. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 2014;13:788–94.
45 Jin YP, Gatz M, Johansson B, *et al*. Sensitivity and specificity of dementia coding in two Swedish disease registries. *Neurology* 2004;63:739–41.
46 Savva GM, Arthur A. Who has undiagnosed dementia? a cross-sectional analysis of participants of the Aging, Demographics and Memory Study. *Age Ageing* 2015;44:642–7.
47 Livingston G, Leavey G, Manela M, *et al*. Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. *BMJ* 2010;341:c4184.

Appendix 2: Search terms used for systematic review and meta-analysis of marital status and risk of dementia

Medline		**exp marital status/ OR marriage.tw. OR married.tw. OR marital status.tw. OR spouse.tw**
	AND	exp Dementia/ **OR** dementia.tw. **OR** alzheimer*.tw
	AND	Epidemiologic studies/ **OR** exp case control studies/ **OR** exp cohort studies/ **OR** Case control.tw. **OR** (cohort adj (study or studies)).tw. **OR** Cohort analy$.tw. **OR** (Follow up adj (study or studies)).tw. **OR** (observational adj (study or studies)).tw. **OR** Longitudinal.tw. **OR** Retrospective.tw. **OR** Cross sectional.tw. **OR** Cross-sectional studies/
Embase		exp marriage/ **OR** marriage.tw. **OR** married.tw. **OR** marital status.tw. **OR** spouse.tw
	AND	exp Dementia/ **OR** dementia.tw. **OR** alzheimer*.tw
	AND	Clinical study/ **OR** Case control study **OR** Case control study **OR** Longitudinal study/ **OR** Retrospective study/ **OR** Prospective study/ **OR** Cohort analysis/ **OR** (Cohort adj (study or studies)).mp. **OR** (Case control adj (study or studies)).tw. **OR** (follow up adj (study or studies)).tw. **OR** (observational adj (study or studies)).tw. **OR** (epidemiologic$ adj (study or studies)).tw. **OR** (cross sectional adj (study or studies)).tw. **NOT** Randomized controlled trials/
PsycINFO		exp marriage/ **OR** marriage.tw. **OR** married.tw. **OR** marital status.tw. **OR** spouse.tw
	AND	exp dementia/ **OR** dementia.mp. **OR** Alzheimer.mp
	AND	exp Longitudinal studies/ **OR** cohort.mp **OR** prospective.mp **OR** longitudinal.mp **OR** retrospective.mp **OR** ((case* adj5 control*) **or** (case adj3 comparison*) **or** case-comparison **or** control group*).ti,ab.id. **NOT** “literature review”.md

Appendix 3: Full data extracted from studies for systematic review and meta-analysis of marital status and risk of dementia

Study	Recruitment source and population at start (response rate) Mean population age at baseline	n of participant at study inception n of cases at follow-up	Mean/ range of years follow-up	n un-explained loss to follow-up / missing data %	Measurements of marital status (%) At what age, and approx. what year was marital status recorded?	Analysis adjusted for:	Statistical model used	Outcome How was dementia assessed?	Results	Adjusted results (95% Confidence interval)	Un-adjusted results
COHORT											
Amieva 2010	PAQUID, France: Longitudinal population-based study of randomly selected older adults (69%) 73.7 years	2089 461 all Dementia	5-15 Cases excluded if dementia detected within 3yr 'latent period'	1264 38%	Married (60.7%) Widowed (32.5%) Divorced (2.7%) Single (4.2%) Assessed for over 65s in 1988	Age; Sex; Edu; baseline cognition; positive affect; ADLs; Chronic diseases; quality and quantity of social network contact	Cox regression (with age as time-scale)	**Dementia**	Married Widowed Divorced Single	HR 1 HR 0.88 (0.7, 1.1) HR 0.94 (0.5, 1.7) HR 1.29 (0.7, 2.1)	Not provided
		373 Alzheimer's Disease						**Alzheimer's Disease** (Clinical assessment by neurologist using valid criteria)	Married Widowed Divorced Single	HR 1 HR 0.92 (0.7, 1.1) HR 0.88 (0.4, 1.7) HR 1.36 (0.7, 2.3)	
Arai 2004	Hokkaido, Japan. Community-based prospective study 69 years	853 34	5	No data provided	Living with spouse 71% Not living with spouse 29% Living with others 15% Assessed in 1998	Age; Sex	Mantel-Haentzel	**Dementia** Clinical assessment based on algorithm	Living with spouse Not living with spouse	RR 1 RR 2.0 (1.0, 5.0)	1 2.2
Bae 2014	Korean Longitudinal Study on Cognitive Aging and Dementia (71.6%) 71.7	359 45 all dementia	3.5	144 40%	Married 70.2% Widowed 29.8% Divorced 0% Single 0% Assessed in 2008	Age, sex	Cox regression	**Dementia**	Married Widowed Divorced Single	HR 1 HR 1.79 (0.5, 6.5) HR 0 HR 0	Not provided
		9 Alzheimer's Disease						**Alzheimer's Disease**	Married Widowed Divorced Single	HR 1 HR 4.40 (0.8, 24.7) HR 0 HR 0	

								Clinical assessment by psychiatrist using valid criteria			
Bickel 1994	Mannheim, Germany. Longitudinal population-based cohort of elderly persons in private households (82.1%) 73.8 years	331 34	7-8	12 4%	Married 42.4% Widowed 47.5% Divorced 3.8% Single 6.4% Assessed in 1992	Age, sex	Cox regression	**Dementia** Clinical assessment by trained physicians based using valid criteria	Married Widowed Divorced Single	HR 1 HR 1.59 (0.7, 3.5) HR 3.17 (0.6, 16.4) HR 2.90 (0.8, 10.5)	1 1.86 3.21 3.56
Fratiglioni 2000	Kungsholmen, Sweden: Longitudinal population-based study of community-dwelling people born before 1913 (76%) 81.5 years	1368 176	3	165 12%	Married 27.8% Widowed 45.4% Divorced 5.9% Single 20.9% Assessed in 1987	Age; Sex; BL cognition	Cox regression	**Dementia** Clinical assessment by 2 independent physicians using valid criteria	Married Widowed Divorced Single	HR 1 HR 1.45 (0.9, 2.2) HR 1.04 (0.5, 2.4) HR 1.77 (1.1, 2.9)	1 1.6 (wid or div) 1.8
Håkansson 2009	CAIDE project. Longitudinal population-based study derived from random sampling in two regions in Eastern Finland (82-90%) 71.3 years	2000 44	20.9	511 2.7%	Married 80.1% Widowed 7.8% Divorced 4.4% Single 7.8% Mid-life – people aged 50.5 between 1972-87 Late life – people aged 71.3 in 1998	Age; Sex; Edu; ApoE; BMI; BP; Cholesterol; Occupation; Physical activity; Region; Smoking; Depression	Logistic regression	**Alzheimer's Disease** Clinical assessment by expert board using valid criteria	*Mid-life marital status* Married Widowed Single/divorced *Mid-and late-life marital status change* Remained married Became single Remained single	 OR 1 OR 2.52 (0.8, 7.7) OR 1.78 (0.7, 4.9) OR 1 OR 1.60 (0.7, 3.8) OR 2.83 (1.1, 7.4)	Not provided
Hatch 2013	Cache County Memory Study. Longitudinal population based study of all residents aged	5092 548 all dementia	12	1459 28.7%	Married 65.9% Widowed 29.9% Divorced 4.1%	Age; Sex; Occupation; ApoE	Cox regression	**Dementia**	Married Widowed Divorced	HR 1 HR 0.99 (0.81, 1.22) HR 0.65 (0.37, 1.16)	1 1.75 0.67

	over 65, identified from Medicare records (90%) 74.6 years	369 Alzheimer's disease			Measured in 1995			**Alzheimer's Disease** (Clinical assessment by expert board using valid criteria)	Married Widowed Divorced	HR 1 HR 1.04 (0.82, 1.33) HR 0.59 (0.28, 1.25)	1 2.05 0.64
Sundström 2014	Betula prospective cohort study, Umeå Sweden: Longitudinal population-based study derived from general population stratified by age and sex. (87%) 74.7 years	1677 354	8.6	32 2%	Married 57.6% Widowed 14.2% Divorced 5.7% Single 32.6% Assessed in 1993-5	Age; Sex; Alcohol; mental illness; availability of a close friend; parental status	Cox regression	**Dementia** Clinical assessment by 2 independent physicians using valid criteria	Married Widowed Divorced Single	1 HR 1.30 (1.0, 1.7) HR 1.32 (0.9, 2.1) HR 1.09 (0.6, 1.9)	 1.42 1.48 1.59
Sundström 2016	Linnaeus database, Sweden: Linked population data from healthcare and death records for entire population 69.4 years (other group of people aged 50-64, mean age 56.1)	750129 25722	6	32065 1%	**Men**: Married 68.1% Widowed 3.5% Divorced 15.0% Single 13.5% **Women**: Married 61.8% Widowed 13.1% Divorced 17.0% Single 8.2% **Total:** Married 64.9% Widowed 8.4% Divorced 16.0% Single 10.8% Assessed in 1997	Age; Sex; Parental status; Edu; Income; CVD	Cox regression	**Dementia** Derived from clinical records or death certificates: Specificity 98% Sensitivity 55%	**All aged 65-74** Married Widowed Divorced Single	 HR 1 HR 1.12 (1.1, 1.2) HR 1.42 (1.4, 1.5) HR 1.23 (1.2, 1.3)	**(Age-adjusted)** 1 1.11 1.42 1.25
									Men aged 65-74 Married Widowed Divorced Single	 HR 1 HR 1.10 (1.0, 1.2) HR 1.47 (1.4, 1.6) HR 1.29 (1.2, 1.4)	**(Age-adjusted)** 1 1.10 1.48 1.32
									Women aged 65-74 Married Widowed Divorced Single	 HR 1 HR 1.10 (1.1, 1.4) HR 1.36 (1.3, 1.4) HR 1.16 (1.1, 1.3)	**(Age-adjusted)** 1 1.11 1.36 1.18
									All aged 50-64 Married Widowed Divorced Single	 HR 1 HR 1.28 (1.1, 1.4) HR 1.79 (1.7, 1.9) HR 1.71 (1.6, 1.9)	Not provided

CASE-CONTROL				Missing data							
Beard 1992	Rochester, USA. Epidemiology Project. Cases selected from records of Mayo Clinic which delivered medical care to most residents. 80.4 years	241 cases 241 controls	N/A	0	Married 28.8% Widowed 48.0% Divorced 5.4% Single 17.8% Assessed at point of diagnosis (1975-79)	Matched by age and sex	Logistic regression	**Alzheimer's Disease** Clinical diagnoses confirmed against valid criteria by psychiatrist.	Married Widowed Divorced Single	OR 1 OR 1.10 (0.7, 1.7) OR 1.25 (0.5, 2.9) OR 1.07 (0.6, 1.8)	Not provided
									Men Married Widowed Divorced Single	 OR 1 OR 1.24 (0.8, 1.8) OR 3.45 (0.9, 14.0) OR 1.73 (0.3, 9.7)	Not provided
									Women Married Widowed Divorced Single	 OR 1 OR 0.98 (0.8, 1.2) OR 0.77 (0.4, 1.4) OR 0.94 (0.7, 1.2)	Not provided
Seidler 2003	Frankfurt, Germany. Cases selected from general practice registers: (77% agreed to participation) Controls selected as random sample of population register >65 years (61%) AND sample from general practice register (90%) Cases: 79.5 years Controls: 75.4 years	195 cases 229 controls	N/A	29 6%	Married 78.5% Widowed 11.1% Divorced 3.8% Single 6.6% Derived in c2001 from interview with patient or next-of-kin based on marital status when 50 yearsrs	Age; sex; edu; region; family history; smoking	Logistic regression	**Dementia** Clinical diagnoses confirmed against valid criteria by psychiatrist.	*Status at 30yrs* Married Widowed Divorced Single	 *OR 1* *OR 2.1 (0.7, 6.2)* *OR 1.0 (0.2, 4.1)* *OR 1.1 (0.6, 2.0)*	 1 2.50 1.14 1.23
									Status at 50 yearsrs Married Widowed Divorced Single	 *OR 1* *OR 1.2 (0.6, 2.3)* *OR 0.6 (0.2, 1.8)* *OR 1.1 0.5, 2.5)*	 1 1.69 0.58 1.36
									Status 10y earlier Married Widowed Divorced Single	 *OR 1* *OR 1.0 (0.6, 1.6)* *OR 0.5 (0.2, 1.7)* *OR 1.7 (0.7, 4.2)*	 1 1.47 0.57 1.99
		108 Alzheimer's disease						**Alzheimer's Disease**	*Status at 30yrs* Married Widowed Divorced Single	 *OR 1* *OR 4.3 (1.4, 12.9)* *OR 1.3 (0.2, 7.2)* *OR 0.7 (0.3, 1.5)*	 1 4.14 1.04 0.99
		59 vascular dementia						**Vascular dementia**	*Status at 30yrs* Married Widowed Divorced Single	 *OR 1* *OR 1.7 (0.2, 14.9)* *OR 1.5 (0.2, 13.7)* *OR 1.7*	 1 0.73 0.92 1.43

CROSS-SECTIONAL				**Missing data**							
Correa Ribeiro 2013	Rio de Janeiro, Brazil. Age and sex-stratified sample selected from clients of a private health-care plan: (98%) 78.2 years	683 115	N/A	108 12.5%	Married 41.6% Widowed 40.8% Divorced 7.5% Single 10.1% Derived from interview by researcher in 2009	Age; Sex; edu; Personal income	Log-binomial regression	**Dementia** Clinical diagnoses by consensus panel on valid criteria	Married Widowed Divorced/separated Single	RR 1 RR 1.43 (0.9, 2.3) RR 0.31 (0.1, 2.0) RR 0.81 (0.3, 2.1)	1 2.97 0.24 1.17
Fan 2015	Taiwan. Nationwide population-based cross-sectional study (36.5%) 75.7 years	10432 929	N/A	419 5.0%	Married 64.2% Widowed 31.0% Divorced/single 4.8% Derived from researcher interview in 2012	Age; sex; edu; BMI; Hypertension; Diabetes; CVD; Smoking; alcohol; exercise; social engagement; sleep	Logistic regression	**Dementia** Clinical diagnoses confirmed against valid criteria by psychiatrist.	Married Widowed Divorced/single	OR 1 OR 1.42 (1.2, 1.8) OR 1.20 (0.7, 2.0)	1 2.65 1.67
Guaita 2015	Abbiategrasso, Italy. Survey of all residents aged 70-74 yr. (80.4%) 71.7 years	1321 39 all dementia	N/A	2 0.2%	Married 67.1% Widowed 24.6% Divorced 2.2% Single 6.1% Assessed in 2011	Age; Sex; Area of birth; Occupation; Education	Logistic regression	**All dementia** Clinical diagnoses confirmed against valid criteria by geriatrician	Married Widowed Divorced Single	RR 1 RR 1.17 (0.5, 2.7) RR 0.87 (0.1, 7.2) RR 2.52 (0.8, 7.8)	1 1.18 1.26 2.44
		15 Alzheimer's disease						**Alzheimer's Disease**	Married Widowed Divorced Single	RR 1 RR 1.05 (0.3, 3.8) RR 2.42 (0.3, 23.0) RR 1.31 (0.2, 11.0)	1 1.18 3.09 1.18
		18 vascular dementia						**Vascular dementia**	Married Widowed Divorced Single	RR 1 RR 1.8 (0.5, 6.2) RR -- RR 5.63 (1.3, 23.8)	1 1.45 -- 1.45
Zhang 2006	China: prevalence study conducted across four different communities. (94%)	34807 732 Alzheimer's Disease	N/A	59 0.1%	Married 77.4% Widowed 20.8% Divorced/single 1.6%	Age; Sex; Edu; Rural/urban dwelling; ethnicity; occupation;	Logistic regression	**Alzheimer's Disease**	Married Widowed Divorced/Single	OR 1 OR 1.4 (1.1, 1.7) OR 2.0 (0.8, 5.0)	1 5.2 2.3

	68.2 years	295 vascular dementia			Assessed in over 55s in 1997	age/region interaction; sex/education interaction		**Vascular Dementia** Consensus panel diagnosis after 3-phase assessment	Married Widowed Divorced/Single	OR 1 OR 0.6 (0.5, 0.9) OR 1.0 (0.4, 2.4)	1 1.1 0.9

Key: ADLs = Activities of daily living; BMI = body mass index; CVD = cardiovascular disease; Edu = education; HR = Hazard ratio; OR = Odds ratio; RR = Risk ratio

Notes: Shaded results are those which have been provided on request by study authors. *Italicised results* are those which I calculated from study data e.g. when confidence intervals were not provided

Appendix 4: Rating criteria for assessing quality of studies and results from quality rating

* Indicates a point for methodological quality

COHORT STUDIES

Selection

1) Representativeness of the exposed cohort
    a. truly representative of the average person over 65 years in the community with initial response rate over 70% *
    b. selected group of users e.g. nurses, volunteers
    c. no description of the derivation of the cohort
2) Selection of the non-exposed cohort
    a. drawn from the same community as the exposed cohort *
    b. drawn from a different source
    c. no description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
    a. secure record (e.g. public records) *
    b. structured questionnaire with details on timing of potential changes of marital status *
    c. written self-report
    d. no description
4) Demonstration that outcome of interest was not present at start of study
    a. yes *
    b. no

Comparability

5) Comparability of cohorts on the basis of the design or analysis (2 * possible)
    a. As well as **age and sex**, the study controls for **Education or baseline cognition***
    b. Study additionally controls for a **measure of physical illness** AND **socio-economic status ***
    c. Only adjusts for **age and sex**

Outcome

6) Assessment of outcome (*dementia*)
    a. Systematic blind assessment using standard diagnostic criteria *
    b. Record linkage
    c. Self- or carer- report
    d. no description
7) Was follow-up long enough for outcomes to occur
    a. At least 5 years *
    b. no
8) Adequacy of follow up of cohorts
    a. complete follow up - all subjects accounted for *
    b. Less than <30 % lost to follow up *
    c. follow up rate < 70% (select an adequate %) and no description of those lost
    d. no statement

		1 *	2 *	3 *	4 *	5 * / **	6 *	7 *	8 *	Total
1	**Amieva**	c	*	d	*	*	*	*	c	**5**
2	**Arai**	c	*	d	*	c	c	*	d	**3**
3	**Bae**	b	*	d	*	c	*	b	c	**3**
4	**Bickel**	b	*	d	*	c	*	*	*	**5**

5	**Fratiglioni**	*	*	d	*	*	*	b	*	**6**
6	**Håkansson**	*	*	d	*	**	*	*	*	**8**
7	**Hatch**	b	*	*	*	**	*	*	*	**5**
8	**Sundström 2014**	*	*	d	*	*	*	*	*	**7**
9	**Sundström 2016**	*	*	*	*	**	b	*	*	**8**

CASE-CONTROL STUDIES

Selection

1) Is the case definition (*dementia diagnosis*) adequate?
    a. yes, with independent validation *****
    b. Record linkage
    c. no description
2) Representativeness of the cases
    a. consecutive or obviously representative series of cases *****
    b. potential for selection biases or not stated
3) Selection of Controls
    a. community controls *****
    b. hospital controls
    c. no description
4) Definition of Controls
    a. no history of disease (endpoint) *****
    b. no description of source

Comparability

e. Comparability of cases and controls on the basis of the design or analysis (2 * possible)
    a. As well as **age and sex**, the study controls for **Education or baseline cognition***
    b. study also controls for a **measure of physical illness** AND **socio-economic status ***
    c. Only adjusts for **age and sex**

Exposure

f. Ascertainment of exposure
    a. secure record (eg public records) *****
    b. structured questionnaire with details on timing of potential changes of marital status AND independent verification (notes OR informant) *
    c. interview not blinded to case/control status
    d. written self-report or medical record only
    e. no description

g. Same method of ascertainment for cases and controls
    a. yes *****
    b. no

h. Non-Response rate
    a. same rate for both groups *****
    b. non respondents described
    c. rate different and no designation

		1 *	**2 ***	**3 ***	**4 ***	**5 * / ****	**6 ***	**7 ***	**8 ***	**Total**
1	**Beard**	b	b	*	b	-	c	*	*	**3**
2	**Seidler**	b	b	b	b	*	c	b	b	**1**

CROSS-SECTIONAL STUDIES

Selection

1) Were the criteria for inclusion in the sample clearly defined?
    a. truly representative of the average person over 65 years in the community *
    b. selected group of users eg volunteers
    c. no description of the derivation of the sample
2) Was the initial response rate reported?
    a. Reported and > 70% *
    b. Reported and < 70%
    c. Not reported

Measurements

3) Ascertainment of exposure
    a. secure record (eg public records) *****
    b. structured questionnaire with details on timing of potential changes of marital status AND independent verification (notes OR informant) *
    c. interview not blinded to dementia status
    d. written self-report or medical record only
    e. no description
4) Assessment of Dementia
    a. Systematic blind assessment using standard diagnostic criteria *
    b. Record linkage *
    c. Self- or carer- report
    d. no description

Comparability

5) Comparability of cases and controls on the basis of the design or analysis (2 * possible)
    a. As well as **age** and **sex**, the study controls for **Education** or **baseline cognition***
    b. study controls for a measure of **physical illness** AND **socio-economic status** *
    c. Only adjusts for **age and sex**

		1 *	**2 ***	**3 ***	**4 ***	**5 * / ** **	**Total**
1	**Correa-Ribeiro**	b	*	c	*	*	**3**
2	**Fan**	*	*	c	*	*	**4**
3	**Guaita**	*	*	c	*	*	**4**
4	**Zhang**	*	*	e	*	*	**4**

Appendix 5: Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008–2016

ELSEVIER

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Alzheimer's & Dementia

Featured Article

Accuracy of general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic accuracy 2008–2016

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Abstract

Introduction: Recognizing dementia in general hospitals allows for tailored care. We aimed to assess hospital dementia diagnosis accuracy, changes over time, and predictors of correct identification.

Method: Retrospective cohort study of people over 65 years, using data from a large mental health care database as gold standard, linked to 2008–2016 English hospital data.

Results: In 21,387 people who had 138,455 admissions, we found sensitivity and specificity of dementia recording, respectively, to be 78.0% and 92.0% for each person's complete records, and 63.3% and 96.6% for each nonelective admission. Diagnostic sensitivity increased between 2008 and 16. Accurate general hospital recording of the presence of dementia was lower in ethnic minority groups, younger, single people, and those with physical illness.

Discussion: Dementia diagnosis recording in general hospitals is increasing but remains less likely in some groups. Clinicians should be aware of this inequity and have a higher index of clinical suspicion in these groups.

Keywords: Diagnosis; Epidemiology; Prevalence; Medical records; Hospital records

1. Introduction

There are increasing numbers of people with dementia [1], and they are more frequently admitted to general hospitals than those without dementia [2], due to their greater burden of physical and mental comorbidity, poorer nutritional status, and difficulties managing medication and seeking timely medical care. In the United Kingdom, around two-thirds of people with dementia are thought to have received a diagnosis [3], but this frequently comes late in the illness [4], which limits the provision of appropriate care and opportunities for patients to make future plans at an early stage. Increasing timely diagnosis is part of many countries' dementia strategy [5], and hospital admission may be an opportunity to improve dementia diagnosis.

Recognition of dementia in hospital inpatients is also important as hospital medical records should accurately reflect the person's clinical condition so that tailored inpatient care and discharge plans can be provided, particularly considering the effect of dementia on existing health conditions [6]. People with dementia may forget the contents of the agreed management plan, and lack of mental capacity means that people with dementia are often unable to make health care decisions [7], potentially requiring others to make decisions according to best interests principles [8].

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Furthermore, understanding the accuracy of dementia diagnoses in general hospitals will also inform clinical research as routine medical records are an increasingly important method of case ascertainment for epidemiological studies. Hospital data in the United Kingdom have been used to address numerous research questions [9–11], but there are concerns about inaccurate or missed diagnoses [12], and previous studies found this to vary according to sociodemographic and clinical characteristics [13]. The sensitivity of dementia reporting in hospital discharge records has been estimated to be 70% in the United States [14], 51% in Finland [15], and between 26% and 43% in Swedish studies [16–18]. These studies have used cohort study assessments or clinical examinations as gold standard, but they have been relatively small, and none have examined data later than 2008 nor examined trends over time. Recent health policy to increase timely diagnosis [19] and greater health care professional awareness of the condition may have increased accuracy of subsequent diagnostic recording.

We sought to investigate the accuracy of recorded diagnoses of dementia in general hospitals in the United Kingdom, using data up to 2016. In particular, we aimed to

1. analyze the sensitivity and specificity of dementia diagnosis recording in general hospitals, using secondary mental health care data as gold-standard diagnostic status;
2. examine time trends in sensitivity and specificity of general hospital dementia diagnosis between 2006 and 2016; and
3. explore sociodemographic and clinical correlates of diagnostic accuracy.

2. Methods

2.1. Ethics statement

The Oxfordshire Research Ethics Committee C (reference 08/H0606/71 + 5) approved the data resources for secondary analysis.

2.2. Study setting and data source

We conducted a retrospective observational study using data from two linked data sets of routinely collected clinical data, described below in sections 2.2.1 and 2.2.2.

2.2.1. The South London and Maudsley National Health Service Foundation Trust Biomedical Research Centre case register "Clinical Record Interactive Search" data extraction tool

The Clinical Record Interactive Search (CRIS) data resource provides pseudonymized electronic medical records from South London and Maudsley, one of Europe's largest secondary mental health care providers, which delivers a range of psychiatric care, including dementia assessment and management in memory clinics to a catchment area containing 1.2 million residents in four South London boroughs. Memory clinics are the primary dementia diagnostic service in the United Kingdom whose practice is to take referrals from other health and social care services (usually primary care) of people who have been identified as having possible dementia. There is no routine dementia screening in the United Kingdom.

In CRIS, pseudonymized data are extracted from structured fields in patients' electronic clinical records and from unstructured text within clinical records (including correspondence and case notes) with a natural language processing algorithm using General Architecture for Text Engineering software [20], which generates text strings associated with diagnostic statements. The accuracy of the General Architecture for Text Engineering software is described in detail in a previous publication [21]; it has been found to have precision of 0.99 for diagnosis. The CRIS data set has been used to examine a variety of dementia-related research questions [22,23]. Data are available for all clinical records from January 1, 2006, and CRIS is linked to the Hospital Episode Statistics (HES) database, described in the following.

2.2.2. National Health Service Digital HES

This data set contains clinical information about National Health Service care, collected directly by hospital providers and has been used in a number of research studies [24–26]. The data of interest for this study are records of general (nonpsychiatric) inpatient admissions to any hospital in England and the clinical diagnoses recorded on each hospital discharge summary by the treating clinical team. Diagnoses are recorded as International Statistical Classification of Diseases and Related Health Problems, 10th Revision [27] codes and each admission has up to 20 diagnostic codes. The method of admission (elective or nonelective) is also recorded [28]. Diagnoses recorded in HES are those clinically identified during the admission, obtained from correspondence with primary care, or derived from preexisting clinical records such as previous hospital medical records—some record systems prepopulate diagnosis fields with previously recorded chronic conditions. There was no routine practice of dementia assessment in English hospitals until 2012 when the U.K. Department of Health recommended case finding in older inpatients for possible dementia, by asking if any person who was admitted had a change in their memory lasting a year to the extent that it influenced functioning. This would be followed, if dementia was suspected, by referral to memory services [29], although we have no data reporting the extent of adoption of this practice.

2.3. Study participants

We retrieved records from CRIS (South London and Maudsley) of all patients aged 65 years or over who had been assessed (as part of ongoing follow-up or as first clinical contact) during the study window from January

1, 2008 to March 31, 2016. We did not include patients whose first electronic record of dementia was during 2006–2007 as we aimed to identify people with newly diagnosed dementia rather than those with a history of the condition. Those whose first CRIS recording was before 2008 would include many whose dementia was diagnosed before the inception of the data set and who were being followed up during 2006–2007. These data were linked to HES records over the same period. All mental health and dementia diagnoses in CRIS were extracted from structured fields in the electronic medical record where clinicians are required to record International Statistical Classification of Diseases and Related Health Problems, 10th Revision [27] codes or from unstructured text using the General Architecture for Text Engineering software, including dementia diagnosis (coded in CRIS as F00x-F03x). We retrieved the dates of, and diagnoses recorded for, each general hospital admission during the study window, including diagnosis of dementia (coded in HES as F00x-F03x, G30x, G31.0, or G31.8). We excluded those who had dementia in their CRIS records but were later diagnosed as having mild cognitive impairment (F06.7), as we judged this to mean these people had the dementia prodrome state [30] rather than clinical dementia.

2.4. Covariates

We extracted data from CRIS on participants' age, sex, ethnicity (white, Asian, black African/Caribbean, or other), marital status, and last recorded dementia subtype (Alzheimer's disease; vascular dementia; Lewy body dementias; other dementia [encompassing any other specified dementia type]; and unspecified dementia [where dementia etiology was not recorded]). We estimated the socioeconomic status from the 2010 Index of Multiple Deprivation, which is based on 37 indicators related to the patient's most recent address [31], with a higher score indicating more socioeconomic deprivation. Dementia severity was estimated from the most recently recorded Mini Mental State Examination (MMSE) [32] score at the time of hospital admission. Other aspects of clinical presentation were derived from CRIS using the Health of the Nation Outcome Scale (HoNOS), which is a standard instrument applied routinely in mental health care with adequate-to-good psychometric properties [33]. It comprises 12 subscale rating problems with agitation; self-injury; alcohol/drug use; cognition; physical illness; hallucinations; depressed mood; relationships; daily living function; living conditions; occupation or activities; other problems. Each domain is rated 0 (no problem) to 4 (severe or very severe problem). As $\geq$2 is seen to indicate a clinically significant problem, we dichotomized the HoNOS scores in each domain to facilitate interpretation: scores of 0 and 1 were grouped as no/minor problems and scores of $\geq$2 indicated problem in that domain. We did not use the cognitive subscale in our primary analyses due to its correlation with MMSE or the "other" subscale due to its nonspecific clinical meaning.

Age, sex, and ethnicity statuses were taken from the baseline recording, and other covariates were recorded at the time closest to the first hospital admission.

2.5. Analytic approach

We used the CRIS database record as the gold-standard definition of dementia because it includes records from the area's memory clinics, which are the principal U.K. dementia diagnostic services [19,34] in which people are assessed by trained psychiatrists in consultation with the broader clinical team. Those not seen in memory clinics would usually have been assessed by psychiatrists in other secondary mental health care services. Included patients were all assessed as part of routine clinical practice. They had all received an International Statistical Classification of Diseases and Related Health Problems, 10th Revision diagnosis of dementia (therefore fulfilling standardized gold-standard criteria) or another mental disorder during the study window. Although formalized dementia screening assessment was not administered to all participants, dementia would have been considered as a differential diagnosis for people aged over 65 years with psychiatric disorder, and those with suspicion of dementia would have received standard diagnostic workup. We henceforth describe as "sensitivity" the proportion of people with dementia in CRIS who are correctly identified as having the condition in HES and as "specificity" the proportion of people without a dementia diagnosis in CRIS who are correctly identified as such in HES.

A single cohort would not be adequate to analyze sensitivity and specificity because CRIS and HES assessments rarely take place simultaneously, and for those with CRIS-diagnosed dementia, the date on onset is uncertain, and for those without such a diagnosis at their last CRIS assessment, we could not be certain that dementia did not develop later. Therefore, we analyzed people with and without a CRIS dementia diagnosis separately. To assess sensitivity, we examined all HES records after the CRIS dementia index date, which was the date of the first dementia diagnosis in the CRIS database and up to March 31, 2016. For specificity, we examined all HES records from January 1, 2008 and before the CRIS index date, which was the date of last assessment in the CRIS database for people without dementia. All statistical analyses were undertaken using STATA 14.2 (2017).

2.5.1. Sensitivity of HES dementia diagnoses

We calculated the following:

1. Sensitivity of HES diagnosis for
   a. each patient (proportion of people with dementia who have dementia recorded in any subsequent HES records);

b. each admission (proportion of admissions of a person with dementia, after their index date, which have dementia recorded in HES); and
c. individual admission records for nonelective admissions only because some patients have multiple repeated admissions for very short elective procedures, for example, renal dialysis or chemotherapy, during which full diagnostic assessment is unlikely to have taken place.

2. Sensitivity of HES diagnosis for nonelective admissions within one year of diagnosis, stratified for year of admission, to evaluate time trends. We restricted this analysis to admissions within 1 year of CRIS dementia diagnosis as we aimed to ensure approximately equal dementia severity for each year in the study window. We judged that allowing a longer gap between CRIS and HES dementia assessment might bias findings due to ease of diagnosis of more severe dementia. We used chi-squared test to examine trend in sensitivity over time.
3. Sociodemographic and clinical predictors of the presence of dementia being correctly recorded in HES for each patient with dementia recorded in CRIS, using logistic regression. Univariate regression for each covariate and then multivariable analysis mutually adjusted for each covariate and for number of general hospital admissions.

2.5.2. *Specificity of HES dementia diagnoses*

We calculated the following:

1. Specificity of HES diagnosis for:
   a. each patient (proportion of people without CRIS-diagnosed dementia for whom dementia is absent in all preceding HES records);
   b. each admission (proportion of admissions of a person without CRIS diagnosed dementia, before their index date, which have dementia absent in HES); and
   c. specificity of individual admission records for nonelective admissions only.
2. Specificity for each nonelective admission of people without dementia, stratified for year of admission, to evaluate time trends. We did not include admissions after March 2015 to ensure all study participants had at least one year of potential CRIS follow-up after hospital admission. Chi-squared test examined trend in sensitivity over time.
3. Sociodemographic and clinical predictors of the absence of dementia being correctly recorded in HES for each patient without CRIS-recorded dementia, using logistic regression. Univariate regression for each covariate and then multivariable analysis mutually adjusted for each covariate and for number of general hospital admissions.

2.5.3. *Additional analyses*

Twenty-seven percent of people with dementia and 61% of people without dementia had missing data on at least one covariate. To avoid a loss of efficiency, we imputed missing covariate values using multiple imputation by chained equations [35]. Five imputed data sets were created using STATA's mi package by replacing missing values with simulated values from a set of imputation models using a model constructed from all potential covariates and outcome variables. We conducted logistic regression on each imputed data set and combined coefficients using Rubin's rules [36].

We conducted a post hoc sensitivity analysis using the cognitive subscale of HoNOS rather than MMSE because of a large amount of missing MMSE data for people without dementia.

3. Results

The study sample comprised 21,387 people. Of these, 8246 had dementia diagnosed in CRIS (South London and Maudsley) during the study period and 13,141 did not. The sociodemographic and clinical characteristics of the study sample and percentage of missing covariate data are summarized in Table 1. The mean age at dementia diagnosis was 82.2 years and 60.4% were female. For the people without dementia, mean age at index date was 77.9 years and 55.4% were female. The majority were from white ethnic background and African/Caribbean people formed the largest ethnic minority group. People in the sample were mostly married or widowed and Alzheimer's disease was the dementia subtype for around half of people with dementia and vascular dementia for a quarter. The median time between dementia diagnosis in CRIS and subsequent general hospital admission was 1.4 years (interquartile range 0.5, 2.7 years), and the time between CRIS assessment of people without dementia and prior general hospital assessment was 1.7 years (interquartile range 0.6, 3.5 years).

3.1. *Sensitivity of general hospital diagnoses of dementia*

Of the 8246 people with dementia who were admitted to hospital, 6429 (sensitivity = 78.0%, 95% confidence interval 77.1, 78.9) had dementia diagnosis at any time in their general hospital records (Table 2). The 8246 people had 37,329 total admissions following their dementia diagnosis during the study period, and the proportion of the individual hospital records that included dementia was 50.3% (49.8, 50.8). Sensitivity for 26,894 nonelective hospital admission records was 63.3% (62.7, 63.9).

Sensitivity of general hospital records within 1 year of CRIS diagnosis increased ($P_{trend} < 0.001$ [chi squared = 87.7, 8 df]) from 48.7% (95% confidence interval 44.3, 53.0) for admissions during 2008 to 61.5% (95% confidence interval 56.5, 66.4) for admissions in 2016 (Fig. 1, full data in Supplementary Appendix A.1).

In the fully adjusted multivariable model (Table 3), independent predictors of a person with dementia having it detected during subsequent general hospital admissions were increasing age, lower MMSE score, having previously recorded agitated behavior, problem with daily activities, and

Table 1
Sociodemographic and clinical characteristics of participants

	People with dementia n = 8246				People without dementia n = 13,141			
	Dementia diagnosed (n = 6429)		Dementia not diagnosed (n = 1817)		Dementia not diagnosed (n = 12,094)		Dementia diagnosed (n = 1047)	
HES record	n	%	n	%	n	%	n	%
Age*								
Mean (SD)	82.6 (6.8)		80.9 (7.4)		77.5 (8.2)		82.2 (7.8)	
65–69	272	9.0	163	4.2	2817	23.3	77	7.4
70–74	675	13.3	241	10.5	2390	19.8	122	11.7
75–79	1266	21.2	386	19.7	2342	19.4	200	19.1
80–84	1720	25.5	464	26.8	2069	17.1	244	23.3
85–89	1671	20.0	363	26.0	1534	12.7	233	22.3
90+	825	11.0	200	12.8	942	7.8	171	16.3
Missing	0		0		0		0	
Sex								
Female	3929	61.1	1053	58.0	6638	54.9	638	60.9
Missing	0		1		2		0	
Ethnicity								
White	5019	78.1	1273	70.1	9153	80.1	790	80.5
Asian	274	4.3	107	5.9	597	5.2	44	4.5
Black African/Caribbean	821	12.8	315	17.3	1232	10.8	108	11.0
Other	189	2.9	86	4.7	450	3.9	39	4.0
Missing	126		36		662		66	
Marital status†								
Married	2020	31.4	587	32.3	3620	33.5	253	27.1
Divorced	460	7.2	167	9.2	1260	11.6	78	8.4
Widowed	2580	40.1	612	33.7	3137	29.0	361	38.7
Single	1053	16.4	338	18.6	2804	25.9	242	25.9
Missing	316		113		1273		113	
Mean deprivation score (SD)†	27.2 (11.2)		27.8 (11.2)		26.8 (11.7)		27.5 (11.4)	
Missing	0		0		0		0	
Mean MMSE (SD)†	18.2 (6.2)		20.2 (5.9)		24.2 (5.5)		20.4 (6.8)	
Missing	870		269		6436		490	
Problem with (from HoNOS subscale)†								
Agitation	1321	20.6	222	12.2	1493	16.6	205	26.2
Self-injury	78	1.2	23	1.3	655	7.3	29	3.7
Alcohol/drugs	150	2.3	62	3.4	574	6.4	31	4.0
Cognition	5647	87.8	1282	70.6	2503	27.9	444	57.8
Physical illness	3895	60.6	1109	61.0	6253	69.4	613	78.5
Hallucinations	787	12.2	187	10.3	1504	16.8	171	22.3
Depressed mood	731	11.4	248	13.7	3408	37.9	252	32.6
Relationships	1064	16.6	257	14.1	1910	21.3	190	24.5
Daily living	4390	68.3	1020	56.1	4413	49.3	5391	70.1
Living conditions	733	11.4	226	12.4	1037	11.8	127	16.9
Occupation/activities	2141	33.3	505	27.8	2553	28.9	273	36.4
Missing‡	294		106		3325		297	
Last recorded dementia diagnosis								
Alzheimer's disease	3373	52.5	796	43.8				
Vascular dementia	1461	22.7	390	21.5				
Lewy body	201	3.1	54	3.0				
Other dementia	443	6.9	133	7.3				
Unspecified	951	14.8	444	24.4				
Median number of hospital admissions (IQR)	4 (2,6)		2 (1,3)		4 (2,8)		6 (3,11)	

Abbreviations: HES, Hospital Episode Statistics; HoNOS, health of the nation outcome scale; IQR, interquartile range; SD, standard deviation; MMSE, Mini Mental State Examination.

*For people with dementia, age is at time of first dementia diagnosis; for people without dementia, age is at time of last assessment.

†Characteristic nearest to first hospital admission.

‡Figure for missing HoNOS score is for the HoNOS domain with most missing information.

Table 2
Sensitivity and specificity of general hospital diagnoses of dementia 2006–2016 for each individual patient and for each individual admission

Sensitivity/specificity assessment	Number of true positives/total with dementia Sensitivity (95% CI)	Number of true negatives/total without dementia Specificity (95% CI)
For each patient	6429 / 8246 78.0% (77.1, 78.9)	12,094 / 13,141 92.0% (91.6, 92.5)
For each admission	18,769 / 37,329 50.3% (49.8, 50.8)	99,302 / 101,126 98.2% (98.1, 98.3)
For each nonelective admission	17,023 / 26,894 63.3% (62.7, 63.9)*	46,973 / 48,650 96.6% (96.4, 96.7)†

Abbreviation: CI, confidence interval.
*Excludes 10,435 elective admissions.
†Excludes 52,476 elective admissions.

having more hospital admissions. People from nonwhite ethnic groups, single people, those with vascular or unspecified dementia, and those with problematic physical health were less likely to have a record of dementia in the HES database. Dementia recording increased with more hospital admissions. The fully adjusted model using a multiply imputed data set yielded similar results (Supplementary Appendix B).

3.2. Specificity of general hospital records

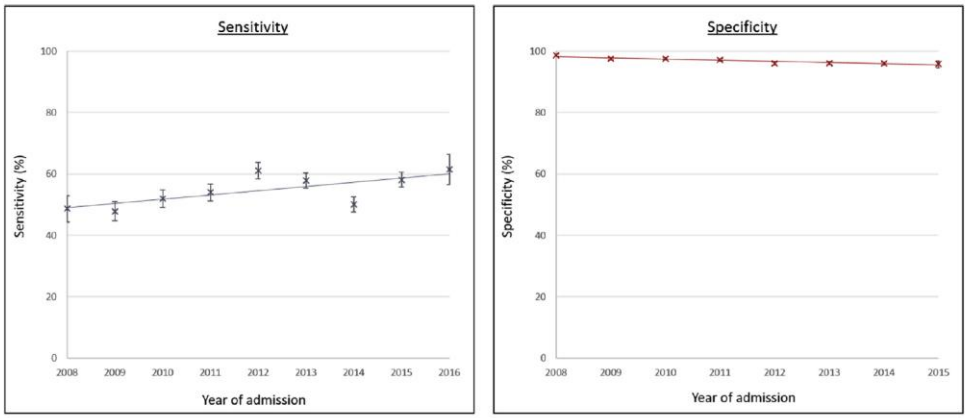
Of the 13,141 people who did not have dementia diagnosed by CRIS (South London and Maudsley) and who were admitted to hospital before their last contact, 12,094 (specificity = 92.0% [91.6, 92.5]) did not have dementia entered at any time in their previous HES records (Table 2). These 13,141 people had 101,126 admissions before their last CRIS assessment, and the proportion of the individual HES records that did not include dementia was 98.2% (98.1, 98.3). Specificity in 48,650 nonelective hospital admission records was 96.6% (96.4, 96.7).

Specificity of HES dementia records has decreased ($p_{trend} < 0.001$ [chi squared = 117.0, 7 df]), with diagnostic specificity for admissions in 2006 being 98.7% (98.3, 99.0) and in 2015 being 95.8% (94.6, 96.8) (Fig. 1, full data in Supplementary Appendix A.2).

In the multivariable analysis (Table 4), dementia was more frequently entered on HES records of people without a CRIS dementia diagnosis if the person was older, had lower MMSE or problems with agitated behavior, activities of daily living or living conditions, and in those with more general hospital admissions. These identified predictors were also found in our sensitivity analyses accounting for missing data using multiple imputation (Supplementary Appendix B) or the cognitive HoNOS subscale rather than MMSE (Supplementary Appendix C).

4. Discussion

In this study examining the accuracy of general hospital diagnoses of dementia, we report that overall sensitivity and specificity of hospital dementia diagnoses were 78.0% and 92.0% for each person's complete hospital records and 63.3% and 96.6% for each individual nonelective hospital admission. The rate of dementia diagnosis in HES is increasing but missed diagnosis is more likely in people who are from ethnic minority groups, single, younger people, and those with better cognitive function, less agitation,



Notes: Sensitivity figures are based on Hospital Episode Statistic (HES) dementia diagnosis during the specified year for non-elective admissions within one year of dementia diagnosis in Clinical Record Interactive Search (CRIS). Sensitivity figures are based on HES dementia diagnosis during the specified year for all non-elective admissions before the final CRIS assessment of a person not diagnosed with dementia.

Fig. 1. Sensitivity and specificity of general hospital dementia diagnoses during nonelective general hospital admissions between 2008 and 2016. Sensitivity figures are based on Hospital Episode Statistic (HES) dementia diagnosis during the specified year for nonelective admissions within 1 year of dementia diagnosis in Clinical Record Interactive Search (CRIS). Sensitivity figures are based on HES dementia diagnosis during the specified year for all nonelective admissions before the final CRIS assessment of a person not diagnosed with dementia.

Table 3
Predictors of the presence of dementia being correctly recorded in general hospital records of people with dementia: Univariate and multivariable logistic regression (n = 8246)

	Univariate analysis		Mutually adjusted multivariable analysis (n = 6037)	
Characteristic	Odds ratio	*P* value	Odds ratio	*P* value
Age (per 1 year increment)	1.03 (1.03, 1.04)	<.001	**1.04 (1.02, 1.04)**	**<.001**
Sex				
Female	1.14 (1.02, 1.27)	.01	1.00 (0.86, 1.17)	.97
Ethnicity				
White	1	<.001	1	**<.001**
Asian	0.65 (0.52, 0.82)		**0.61 (0.45, 0.83)**	
Black African/Caribbean	0.66 (0.57, 0.76)		**0.57 (0.47, 0.69)**	
Other	0.56 (0.43, 0.72)		**0.53 (0.37, 0.75)**	
Marital status				
Married	1	<.001	1	.17
Divorced	0.80 (0.66, 0.98)		0.89 (0.69, 1.14)	
Widowed	1.23 (1.08, 1.39)		0.98 (0.82, 1.17)	
Single	0.91 (0.78, 1.06)		**0.81 (0.67, 0.99)**	
Deprivation score (per 10-unit increase in deprivation)	0.95 (0.91, 1.00)	.04	0.94 (0.89, 1.01)	.08
MMSE (per 1-unit decrease)	1.09 (1.08, 1.10)	<.001	**1.10 (1.09, 1.11)**	**<.001**
Problem with (from HoNOS subscale)*				
Agitation	1.84 (1.58, 2.15)	<.001	**1.65 (1.31, 2.07)**	**<.001**
Self-injury	0.95 (0.59, 1.51)	.82	0.72 (0.37, 1.40)	.33
Alcohol/drugs	0.67 (0.49, 0.90)	.008	0.79 (0.52, 1.20)	.27
Physical illness	0.95 (0.85, 1.06)	.34	**0.74 (0.63, 0.86)**	**<.001**
Hallucinations	1.20 (1.01, 1.42)	.04	1.12 (0.88, 1.42)	.35
Depressed mood	0.80 (0.68, 0.93)	.005	0.93 (0.75, 1.15)	.49
Relationships	1.19 (1.02, 1.37)	.03	0.95 (0.76, 1.18)	.64
Daily living	1.68 (1.50, 1.87)	<.001	**1.43 (1.22, 1.69)**	**<.001**
Living conditions	0.89 (0.76, 1.04)	.14	0.85 (0.68, 1.05)	.14
Occupation/activities	1.28 (1.14, 1.44)	<.001	1.10 (0.93, 1.29)	.28
Last recorded dementia diagnosis				
Alzheimer's disease	1	<.001	1	**<.001**
Vascular dementia	0.88 (0.77, 1.01)		**0.76 (0.63, 0.91)**	
Lewy body dementia	0.88 (0.64, 1.20)		0.99 (0.65, 1.50)	
Other dementia	0.79 (0.64, 0.97)		0.98 (0.74, 1.29)	
Unspecified dementia	0.51 (0.44, 0.58)		**0.41 (0.34, 0.50)**	
Number of admissions (per additional admission)	1.15 (1.13, 1.18)	<.001	**1.17 (1.14, 1.20)**	**<.001**

Abbreviations: HoNOS, Health of the nation outcome scales; MMSE, Mini Mental State Examination.
*HoNOS subscale, dichotomized to 0–1 (no or minor problem) and 2–4 (problem behavior); bold figures indicate $P < .05$ in multivariable analysis.

or activity of daily living impairment, and with more physical illness. Dementia being entered on HES records for a person who is subsequently assessed by secondary mental health care services without dementia being recorded is also becoming more common over time and is more likely with older age, worse cognitive function and problem with agitation, daily living activities, or living conditions. Having more hospital admissions was associated with higher rate of dementia recording.

Our sensitivity estimates are similar to other studies [14–18]. Previous studies have indicated milder dementia is less likely to be detected in data sources [37–40], while being married [40], female, or living in a care home has also been found to increase the chance of dementia being diagnosed. Our study, in a more ethnically diverse population, adds that unrecorded dementia diagnosis in general hospitals is particularly likely for people from ethnic minority groups, who are around half as likely to have a record of dementia. For some, this may be because of impaired communication between them or their family and the assessing clinician [41]. As dementia awareness is lower in minority ethnic groups [42], patients and their families may be less likely to report the emergence of dementia, and clinicians may misattribute symptoms. Our findings suggest that further efforts are required by clinicians in general hospitals to identify dementia cases in people from minority ethnic groups, by reducing language barrier through use of interpreters, using culturally appropriate cognitive assessments, and potentially targeted case finding. The increased risk of missed diagnosis in the presence of physical illness suggests dementia may be misattributed to physical comorbidity. Our findings that unrecorded diagnosis is also more likely in younger people and those with better cognition and activities of daily living

Table 4
Predictors of the absence of dementia being correctly recorded in general hospital records of people without dementia: Univariate and multivariable logistic regression (n = 12,094)

	Univariate analysis		Mutually adjusted multivariable analysis (n = 5187)	
Characteristic	Odds ratio	*P* value	Odds ratio	*P* value
Age (per 1 year increment)	0.94 (0.93, 0.94)	<.001	**0.97 (0.95, 0.98)**	**<.001**
Sex				
Female	0.78 (0.69, 0.89)	<.001	0.93 (0.75, 1.15)	.49
Ethnicity				
White	1	.80	1	.97
Asian	1.17 (0.85, 1.60)		1.06 (0.65, 1.73)	
Black African/Caribbean	0.98 (0.80, 1.21)		0.94 (0.70, 1.28)	
Other	1.00 (0.71, 1.39)		1.04 (0.57, 1.88)	
Marital status				
Married	1	<.001	1	.80
Divorced	1.13 (0.87, 1.47)		0.99 (0.69, 1.43)	
Widowed	0.61 (0.51, 0.72)		0.95 (0.73, 1.25)	
Single	0.81 (0.67, 0.97)		0.87 (0.66, 1.16)	
Deprivation score (per 10-unit increase in deprivation)	0.95 (0.90, 1.00)	.06	1.01 (0.92, 1.10)	.90
MMSE (per 1 unit decrease)	0.91 (0.90, 0.92)	<.001	**0.92 (0.91, 0.93)**	**<.001**
Problem with (from HoNOS subscale)*				
Agitation	0.56 (0.47, 0.66)	<.001	**0.70 (0.54, 0.91)**	**.008**
Self-injury	2.03 (1.39, 2.97)	<.001	1.64 (0.96, 2.79)	.07
Alcohol/drugs	1.64 (1.14, 2.28)	.008	1.50 (0.90, 2.50)	.12
Physical illness	0.62 (0.52, 0.74)	<.001	1.09 (0.85, 1.41)	.48
Hallucinations	0.70 (0.59, 0.84)	<.001	0.86 (0.66, 1.11)	.24
Depressed mood	1.26 (1.08, 1.48)	.003	1.01 (0.81, 1.26)	.92
Relationships	0.83 (0.70, 0.99)	.04	0.97 (0.75, 1.26)	.82
Daily living	0.41 (0.35, 0.49)	<.001	**0.66 (0.52, 0.84)**	**.001**
Living conditions	0.66 (0.54, 0.81)	<.001	**0.71 (0.54, 0.94)**	**.02**
Occupational function	0.71 (0.61, 0.83)	<.001	1.01 (0.81, 1.29)	.87
Number of admissions (per additional admission)	0.96 (0.95, 0.97)	<.001	**0.94 (0.93, 0.95)**	**<.001**

Abbreviations: HoNOS, Health of the nation outcome scales; MMSE, Mini Mental State Examination.
*HoNOS subscale, dichotomized to 0–1 (no or minor problem) and 2–4 (problem behavior); bold figures indicate $P < .05$ in multivariable analysis.

suggest that milder dementia is more often missed. The presence of agitation was probably associated with diagnostic recording as this symptom in an older person can be a trigger for thorough dementia assessment despite the absence of overt cognitive symptoms. We found that single people are less likely to have dementia detected, consistent with previous research findings [13], likely due to the absence of an informant's collateral history. Particular effort should be made to seek supporting information from informants in these groups, and inability to obtain such information should not preclude thorough diagnostic assessment.

Our novel finding of increasing general hospital recording of dementia is important, as recognition of dementia during hospital admissions allows the clinical team to make appropriate adjustments to their communication style, incorporate family members views on health care decisions, initiate specific treatment for dementia's symptoms and consider the effects of dementia on management of other comorbid conditions. The observed increase in recording probably reflects increasing health care professional awareness of dementia, increasing coding accuracy [22,43] and greater communication between primary and secondary care. Furthermore, efforts in 2012 by the UK Department of Health to increase diagnosis rates in secondary care by case finding in older admitted people [29] may have also increased diagnosis in general hospitals, as supported by our finding of increased diagnostic sensitivity during that year.

Our specificity estimate of 92% was lower than figures of 98% [18] and 99% [16] from other studies. However, our analysis of specificity should be interpreted with caution, and the true figure may in fact be higher. Our analysis is based on a cohort of people in contact with secondary mental health care services who may be more likely than a general population to have symptoms resembling dementia. "False-positive" dementia diagnosis (i.e., diagnosis in HES when later assessment did not result in dementia diagnosis in CRIS) is a possible unintended consequence of the drive for earlier dementia diagnosis and potentially harmful. However, we found that older age, worse cognitive function, and problem with daily living activities and agitation predicted "false-positive" recording of dementia, and these are hallmarks of dementia, so some of these may actually represent correct diagnosis of dementia in the general hospital and

incorrect diagnosis (i.e., failure to detect dementia) by CRIS, in which case the specificity is underestimated.

4.1. Strengths and limitations

This is the largest and most up-to-date analysis of hospital register dementia diagnoses, with sufficient data to allow the first analysis of changes in accuracy over time. We used a very large secondary care mental health register as gold standard against which to test accuracy of general hospital diagnosis, with natural language processing used to increase the accuracy of the CRIS register by picking up people whose diagnosis had been written in text records rather than in structured diagnosis fields.

Missed dementia in the CRIS record is possible, although it is based upon the assessment of trained psychiatrists from dementia services. We therefore restricted our sample to people aged over 65 years whom the mental health care service would have been likely to assess for dementia. As the CRIS data source is retrospective, we are not able to validate its accuracy by assessing participants, as used in other studies [44] as it would rely on information, in particular collateral history and cognitive examination, obtained for individual patients. Records are likely to be written in a way that reflects the clinician's overall clinical impression. Missed dementia diagnosis in CRIS may mean that sensitivity in this study is overestimated—we expect that people with dementia whose condition was missed in CRIS would also be more likely to have missed diagnosis in HES—and that specificity may be underestimated, as described previously.

National dementia recording rates are estimated to be around 72%, and estimates for people in this study's catchment area are similar (75%) [3], meaning that CRIS records will miss people with dementia because they have not presented to services. For individuals never seen in secondary mental health care services, therefore not in our CRIS cohort, HES diagnostic sensitivity may be worse as they may be more likely to have characteristics associated with lack of HES dementia recording. Finally, our sample was derived from a specific region in urban and suburban London, which could limit representativeness. However, this area has considerable ethnic and socioeconomic diversity, which allowed us to examine the effect of these factors on dementia recording, and the hospital records were from all of England, so our results are likely to reflect a range of hospital diagnostic practice.

4.2. Clinical implications and future research

UK efforts to increase dementia diagnosis rates in general hospitals have had success, but there is lower recording rates in some groups, likely due to communication difficulties, lack of an informant, or the presence of other causes of cognitive decline. It is therefore important that clinicians are aware of this inequity, and that they have a higher index of suspicion in these patient groups. Policymakers should consider more targeted case-finding approaches and providing training for hospital clinicians in dementia detection in these patient groups. Better sharing of diagnostic information between health care providers, such as automatic population of hospital databases with previously diagnosed conditions, would increase clinician awareness of comorbid conditions including dementia. Future prospective research should seek to identify in more detail the effect of factors such as native language, the presence of an informant, and physical comorbidities on dementia diagnostic accuracy.

Our study also clarifies the validity of hospital episode statistics as a tool for epidemiological and clinical research, and we found higher sensitivity than previous studies. We note the dynamic of increasing dementia recording over the past 9 years and that more hospital admissions improve diagnostic accuracy. However, using HES for case ascertainment may create systematic bias, especially with people from ethnic minorities, in whom dementia will be underestimated. These factors should be taken into consideration when researchers use these records.

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Authors' contributions: A.S., G. Lewis and G. Livingston conceived the idea for this study and designed the analysis plan with input from all authors. A.S. conducted the literature search and conducted the data analysis plan, with input from all other authors. The article and figures were drafted by A.S. with input from G.P., A.S.-M., G. Lewis, R.S. and

G. Livingston. All authors read and approved the final article.

Due to the data management requirements of the pseudonymized data source, no additional data are available for sharing.

The lead author affirms that this article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. The lead author in this statement is the study guarantor.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.02.012.

RESEARCH IN CONTEXT

1. Systematic review: We systematically searched the literature and found six studies examining general hospital record dementia diagnostic accuracy, using data from before 2008, with sensitivity between 28% and 70% and specificity between 94% and 99%.
2. Interpretation: Our study is the largest and most recent analysis. The sensitivity and specificity of general hospital dementia diagnoses was 78.0% and 92.0%, respectively, for each person's complete hospital records and 63.3% and 96.6% for individual hospital admissions. Dementia recording increased between 2008 and 2016. Dementia was more likely to be missed in minority ethnic, older, single people, and in those with milder dementia, non-Alzheimer's dementias, or physical illness.
3. Future directions: Clinicians should be aware of groups less likely to be accurately diagnosed. Future research should test whether training in diagnostic challenge in these groups can improve practice and reduce inequity. Future epidemiological studies using hospital dementia diagnoses should be aware of potential for systematic bias in these databases.

References

[1] Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, Shipley MJ, Muniz-Terrera G, Singh-Manoux A, et al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. BMJ 2017;358:j2856.

[2] Shenkin SD, Russ TC, Ryan TM, MacLullich AM. Screening for dementia and other causes of cognitive impairment in general hospital inpatients. Age Ageing 2014;43:166–8.

[3] NHS England. Dementia Diagnosis Monthly Workbook. Available at: https://www.england.nhs.uk/mental-health/dementia/monthly-workbook/; 2017. Accessed March 30, 2017.

[4] Rait G, Walters K, Bottomley C, Petersen I, Iliffe S, Nazareth I. Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ 2010;341:c3584.

[5] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673–734.

[6] Jackson TA, Gladman JR, Harwood RH, MacLullich AM, Sampson EL, Sheehan B, et al. Challenges and opportunities in understanding dementia and delirium in the acute hospital. PLoS Med 2017;14:e1002247.

[7] Livingston G, Leavey G, Manela M, Livingston D, Rait G, Sampson E, et al. Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. BMJ 2010;341:c4184.

[8] Office of the Public Guardian. Mental Capacity Act 2005: UK Government. Available at: http://www.legislation.gov.uk/ukpga/2005/9/introduction; 2005. Accessed March 30, 2017.

[9] Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, et al. Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study. JAMA Psychiatry 2017;74:712–8.

[10] Wotton CJ, Goldacre MJ. Associations between specific autoimmune diseases and subsequent dementia: retrospective record-linkage cohort study, UK. J Epidemiol Community Health 2017;71:576–83.

[11] Tropea J, LoGiudice D, Liew D, Gorelik A, Brand C. Poorer outcomes and greater healthcare costs for hospitalised older people with dementia and delirium: a retrospective cohort study. Int J Geriatr Psychiatry 2017;32:539–47.

[12] De Lusignan S, Khunti K, Belsey J, Hattersley A, Van Vlymen J, Gallagher H, et al. A method of identifying and correcting miscoding, misclassification and misdiagnosis in diabetes: a pilot and validation study of routinely collected data. Diabet Med 2010;27:203–9.

[13] Savva GM, Arthur A. Who has undiagnosed dementia? A cross-sectional analysis of participants of the aging, demographics and memory study. Age Ageing 2015;44:642–7.

[14] Knopman DS, Petersen RC, Rocca WA, Larson EB, Ganguli M. Passive case-finding for Alzheimer's disease and dementia in two U.S. communities. Alzheimers Dement 2011;7:53–60.

[15] Solomon A, Ngandu T, Soininen H, Hallikainen MM, Kivipelto M, Laatikainen T. Validity of dementia and Alzheimer's disease diagnoses in Finnish national registers. Alzheimers Dement 2014;10:303–9.

[16] Dahl A, Berg S, Nilsson SE. Identification of dementia in epidemiological research: a study on the usefulness of various data sources. Aging Clinical Exp Res 2007;19:381–9.

[17] Feldman A, Rizzuto D, Narasimhalu K, Dahl A, Johansson A, Gregorio M, et al. Validity of dementia diagnoses in two Swedish health registers. Alzheimers Dement 2012;8:P493.

[18] Jin YP, Gatz M, Johansson B, Pedersen NL. Sensitivity and specificity of dementia coding in two Swedish disease registries. Neurology 2004;63:739–41.

[19] Department of Health. Living well with dementia: A National Dementia Strategy 2009. London, UK: Department of Health; 2009.

[20] Cunningham H. GATE, a general architecture for text engineering. Comput Humanities 2002;36:223–54.

[21] Perera G, Broadbent M, Callard F, Chang C-K, Downs J, Dutta R, et al. Cohort profile of the South London and Maudsley NHS Foundation trust biomedical research centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open 2016;6:e008721.

[22] Perera G, Stewart R, Higginson IJ, Sleeman KE. Reporting of clinically diagnosed dementia on death certificates: retrospective cohort study. Age Ageing 2016;45:668–73.

[23] Ward G, Perera G, Stewart R. Predictors of mortality for people aged over 65 years receiving mental health care for delirium in a South

London Mental Health Trust, UK: a retrospective survival analysis. Int J Geriatr Psychiatry 2015;30:639–46.
[24] Aylin P, Alexandrescu R, Jen M, Mayer E, Bottle A. Day of week of procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics. BMJ 2013;346:f2424.
[25] Gunnell D, Metcalfe C, While D, Hawton K, Ho D, Appleby L, et al. Impact of national policy initiatives on fatal and non-fatal self-harm after psychiatric hospital discharge: time series analysis. Br J Psychiatry 2012;201:233–8.
[26] Kapur N, Hunt I, Windfuhr K, Rodway C, Webb R, Rahman M, et al. Psychiatric in-patient care and suicide in England, 1997 to 2008: a longitudinal study. Psychol Med 2013;43:61–71.
[27] World Health Organization. International Statistical Classification of Diseases and Health Related Problems (The) ICD-10 2004. Geneva, Switzerland: World Health Organization; 2004.
[28] Health and Social Care Information Centre. HES Data Dictionary: Admitted Patient Care; 2017.
[29] Department of Health. Using the Commissioning for Quality and Innovation (CQUIN) payment framework Guidance on new national goals for 2012-13 2012. London, UK: Department of Health; 2012.
[30] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.
[31] Department for Communities and Local Government. English Indices of Deprivation 2015. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015; 2015. Accessed March 30, 2017.
[32] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[33] Pirkis JE, Burgess PM, Kirk PK, Dodson S, Coombs TJ, Williamson MK. A review of the psychometric properties of the Health of the Nation Outcome Scales (HoNOS) family of measures. Health Qual Life Outcomes 2005;3:76.
[34] Burns A, Wilkinson A, Peachey S. Best Practice in Memory Services: Learning From Across England 2014. London, UK: NHS England; 2014.
[35] Oudshoorn CGM, Buuren S, Rijckevorsel JLA. Flexible Multiple Imputation by Chained Equations of the AVO-95 Survey. Leiden, The Netherlands: TNO Prevention and Health Leiden; 1999.
[36] Rubin DB. Multiple Imputation for Nonresponse in Surveys 2004. Chichester, UK: John Wiley & Sons; 2004.
[37] Valcour VG, Masaki KH, Curb JD, Blanchette PL. The detection of dementia in the primary care setting. Arch Intern Med 2000;160:2964–8.
[38] Löppönen M, Räihä I, Isoaho R, Vahlberg T, Kivelä S-L. Diagnosing cognitive impairment and dementia in primary health care–a more active approach is needed. Age Ageing 2003;32:606–12.
[39] Ólafsdóttir M, Skoog I, Marcusson J. Detection of dementia in primary care: the Linköping study. Dement Geriatr Cogn Disord 2000;11:223–9.
[40] Wilkins CH, Wilkins KL, Meisel M, Depke M, Williams J, Edwards DF. Dementia undiagnosed in poor older adults with functional impairment. J Am Geriatr Soc 2007;55:1771–6.
[41] LoGiudice D, Hassett A, Cook R, Flicker L, Ames D. Equity of access to a memory clinic in Melbourne? Non-English speaking background attenders are more severely demented and have increased rates of psychiatric disorders. Int J Geriatr Psychiatry 2001;16:327–34.
[42] Mukadam N, Cooper C, Livingston G. A systematic review of ethnicity and pathways to care in dementia. Int J Geriatr Psychiatry 2011;26:12–20.
[43] Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. J Public Health 2011;34:138–48.
[44] Norton MC, Fauth E, Clark CJ, Hatch D, Greene D, Pfister R, et al. Family member deaths across adulthood predict Alzheimer's disease risk: The Cache County Study. Int J Geriatr Psychiatry 2016;31:256–63.

Appendix 6a: Sensitivity and specificity of admission-level general hospital records of dementia, stratified for the year of admission (2008-2016)

Sensitivity

Sensitivity				
Year of hospital admission	Number of non-elective general hospital admissions of people with dementia, ≤1 year following diagnosis	Number of times dementia recorded in HES	**Sensitivity**	**(95% CI)**
2008	528	257	**48.7**	**44.3, 53.0**
2009	969	464	**47.9**	**44.7, 51.1**
2010	1161	604	**52.0**	**49.1, 54.9**
2011	1281	692	**54.0**	**51.3, 56.8**
2012	1430	874	**61.1**	**58.5, 63.7**
2013	1552	898	**57.9**	**55.4, 60.3**
2014	1539	771	**50.1**	**47.6, 52.6**
2015	1627	946	**58.1**	**55.7, 60.6**
2016	387	238	**61.5**	**56.5, 66.4**

Specificity				
Year of hospital admission	Number of non-elective hospital admissions of people without dementia, before last assessment	Number of times dementia absent from HES record	**Specificity**	**(95% CI)**
2008	4647	4585	**98.7**	**98.3, 99.0**
2009	6305	6149	**97.5**	**97.1, 97.9**
2010	6343	6184	**97.5**	**97.1, 97.9**
2011	6450	6272	**97.2**	**96.8, 97.6**
2012	6648	6384	**96.0**	**95.5, 96.5**
2013	6484	6232	**96.1**	**95.6, 96.6**
2014	5861	5628	**96.0**	**95.5, 96.5**
2015	1268	1215	**95.8**	**94.6, 96.8**

Notes: Sensitivity figures are based on Hospital Episode Statistic (HES) dementia diagnosis during the specified year for non-elective admissions within one year of Clinical Record Interactive Search (CRIS) dementia diagnosis. Sensitivity figures are based on HES dementia diagnosis during the specified year for all non-elective admissions before the final CRIS assessment of a person not diagnosed with dementia.

Key: CI = Confidence interval; HES = Hospital Episode Statistic

Appendix 7: Predictors of dementia correctly ever being recorded in general hospital records of people with dementia (true positives) and dementia correctly never being recorded in general hospital records of people without dementia (true negatives): multivariate logistic regression using multiple imputation

Characteristic		True Positives		True negatives	
		Odds Ratio	p-value	Odds Ratio	p-value
Marital status	Married	1		1	
	Divorced	0.94 (0.76, 1.18)	0.61	1.01 (0.77, 1.31)	0.96
	Widowed	1.02 (0.88, 1.18)	0.77	0.97 (0.81, 1.15)	0.70
	Single	0.91 (0.76, 1.08)	0.28	0.95 (0.78, 1.15)	0.61
Number of admissions [a]		**1.19 (1.17, 1.22)**	**< 0.001**	**0.95 (0.94, 0.96)**	**< 0.001**
Age (per 1 year increment)		**1.03 (1.02, 1.04)**	**< 0.001**	**0.94 (0.93, 0.95)**	**< 0.001**
Sex	Female	1.05 (0.93, 1.19)	0.39	**0.87 (0.75 1.00)**	**0.05**
Ethnicity	White	1		1	
	Asian	**0.67 (0.52, 0.85)**	**0.001**	0.98 (0.71, 1.36)	0.92
	Black	**0.63 (0.54, 0.74)**	**< 0.001**	1.02 (0.82, 1.28)	0.84
	Other	**0.63 (0.47, 0.83)**	**0.001**	0.83 (0.57, 1.20)	0.31
Deprivation score [b]		**0.95 (0.90, 1.00)**	**0.04**	0.98 (0.92, 1.04)	0.46
MMSE (per 1 unit decrease)		**1.06 (1.05, 1.07)**	**< 0.001**	**0.95 (0.94, 0.96)**	**< 0.001**
Problem with (from HoNOS domain) [c]:	Agitation	**1.68 (1.74, 2.00)**	**< 0.001**	**0.73 (0.61, 0.88)**	**0.001**
	Self-injury	0.79 (0.47, 1.31)	0.36	**1.52 (1.04, 2.24)**	**0.03**
	Problem-drink/drugs	0.74 (0.53, 1.04)	0.09	1.20 (0.76, 1.92)	0.42
	Physical illness	**0.74 (0.65, 0.85)**	**<0.001**	1.15 (0.96, 1.38)	0.12
	Hallucinations	1.04 (0.86, 1.25)	0.71	0.86 (0.72, 1.03)	0.10
	Depressed mood	**0.78 (0.65, 0.93)**	**0.005**	1.15 (0.98, 1.36)	0.08
	Relationships	0.95 (0.80, 1.12)	0.52	0.97 (0.78, 1.19)	0.74
	Daily living	**1.46 (1.27, 1.68)**	**< 0.001**	**0.71 (0.58, 0.88)**	**0.002**
	Living conditions	0.87 (0.73, 1.04)	0.13	**0.78 (0.62, 1.00)**	**0.05**
	Occupation/activities	1.10 (0.96, 1.26)	0.16	0.98 (0.83, 1.16)	0.83
Last recorded dementia diagnosis	Alzheimer's Disease	1			
	Vascular dementia	**0.80 (0.69, 0.93)**	**0.003**		
	Lewy body dementia	0.94 (0.67, 1.32)	0.72		
	Other dementia	0.85 (0.68, 1.06)	0.14		
	Unspecified dementia	**0.45 (0.38 0.52)**	**< 0.001**		

Key: HoNOS = Health of the nation outcome scales; MMSE = Mini-mental state examination
Notes: [a] Per additional admission; [b] per 10 unit increase in index of multiple deprivation; [c] HoNOS subscale, dichotomised to 0-1 (no or minor problem) and 2-4 (problem behaviour); Bold figures indicate p<0.05 in multivariable analysis

Appendix 8: Hospitalisation of people with dementia: evidence from English electronic health records from 2008 to 2016

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NEURO-EPIDEMIOLOGY

Hospitalisation of people with dementia: evidence from English electronic health records from 2008 to 2016

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Abstract

Hospitalisation of people with dementia is associated with adverse outcomes and high costs. We aimed to examine general, i.e. non-psychiatric, hospitalisation rates, changes since 2008 and factors associated with admission. We also aimed to compare admission rates of people with dementia with age-matched people without dementia. We conducted a cohort study of adults ≥ 65 years, with dementia diagnosed during the 2008–2016 study window, derived from a large secondary mental healthcare database in South London, UK. We used national general hospital records to identify emergency and elective hospitalisations. We calculated the cumulative incidence and rate of hospitalisation and examined predictors of hospitalisation using negative binomial regression, with multiple imputation for missing covariate data. We calculated age-standardised admission ratio for people with dementia compared to those without. Of 10,137 people, 50.6% were admitted to hospital in the year following dementia diagnosis and 75.9% were admitted during median 2.5 years follow-up. Annual admission rate was 1.26/person-year of which 0.90/person-year were in emergency. Emergency hospitalisation rate increased throughout the study period. Compared to controls without diagnosed dementia in the catchment area, the age-standardised emergency admission ratio for people with dementia was 2.06 (95% CI 1.95, 2.18). Male, older, white and socio-economically deprived people and those with clinically significant comorbid physical illness, depressed mood, activity of daily living or living condition problems had more hospitalisations. Emergency hospitalisations of people with dementia are higher than those without, and increasing. Many factors associated with admission are social and psychological, and may be targets for future interventions that aim to reduce avoidable admissions.

Keywords Dementia · Hospitalization · Health services · Prognosis · Geriatrics

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Introduction

Although age-specific incidence of dementia is falling in the US [1] and UK [2], overall numbers affected are rising due to population ageing [2]. Management of people with dementia in general hospitals is challenging as they often have neuropsychiatric symptoms [3], multi-morbidity [4], and difficulty engaging with management plans [5]. People with dementia receive more antipsychotics and sedatives [6], have longer and costlier hospital admissions [7, 8], and often decline during admission [9]. Therefore reducing admissions, many of which may be avoidable [10], would be advantageous for the patient and care-provider. Understanding the correlates of admission of people with dementia would help us to understand the factors leading to admission.

Previous studies examining hospitalisation in dementia have used research samples which under-represent [11, 12] or exclude [13, 14] more severe dementia or physical illness so have limited generalisability. Other studies have been small [13–18], with short follow-up [7, 13, 19, 20]. Many have ascertained admission information from carers [13, 14] resulting in recall bias, or local hospital registers with limited generalisability [15, 19, 21]. No previous study has examined hospitalisation trends, yet there has been increased focus on improving interventions for dementia in recent years [22]. Our study includes all people with dementia within a large secondary healthcare service including memory clinics, the principal diagnostic services to which people with suspected dementia are referred [23], therefore is representative of people with dementia, and uses national hospitalisation register data.

We aimed to:

1. describe general hospital admission rates within the national health care provider in people with dementia diagnosed in secondary mental healthcare services
2. compare admission rates with an age-standardised control population without dementia
3. identify factors associated with hospitalisation, including time trends between 2008 and 2016.

Methods

Study design and data sources

We conducted a cohort study using two linked clinical datasets, described below.

The South London and Maudsley (SLaM) National Health Service (NHS) Foundation Trust Case Register "Clinical Record Interactive Search" (CRIS) data extraction tool.

We used the CRIS resource [24] to identify dementia cases for our cohort. It provides research access to anonymised electronic medical records from SLaM, which provides mental healthcare including dementia assessment and management [25] for a London, UK, catchment area containing 1.2 million residents. CRIS enables anonymised data extraction from structured record fields, and unstructured text data using natural language processing algorithms [24, 26] developed using General Architecture for Text Engineering (GATE) software [27].

The Oxfordshire Research Ethics Committee C (reference 08/H0606/71 + 5) approved use of the data resources for secondary analysis.

NHS Digital Hospital Episode Statistics (HES).

We collected hospitalisation data from HES, which records all English NHS hospitalisation data collected by hospital providers [28]. We used records of general (non-psychiatric) admissions, identified with codes for emergency (unplanned) and elective (planned, e.g. for surgery, renal dialysis, chemotherapy) admissions. At the time of analysis, data were available until 31 March 2016.

Study participants

We retrieved records from CRIS of all patients aged ≥ 65 years who had a diagnosis of dementia entered for the first time on their electronic medical record during the study window from 1 January 2008 to 31 March 2015. We excluded patients whose first electronic record of dementia preceded 2008, as we aimed to include those with newly-diagnosed dementia and patients first diagnosed after March 2015 to ensure all had at least 1 year potential HES follow-up.

We derived dementia status using either structured ICD-10 [29] diagnosis fields (codes F00x-F03x) or unstructured text, using a GATE-derived algorithm, which has been found to have precision 99% and recall 98% for dementia diagnosis [24]. Of the 10,137 patients with dementia, 2970 (29.3%) were ascertained using GATE alone, with similar characteristics to those with ICD-10 diagnosis (eTable 1).

Hospitalisation data for people with dementia were generated by linking people with dementia diagnosed in CRIS to HES admission data; we retrieved the dates of each hospitalisation after the first CRIS-recorded dementia diagnosis until death or 31 March 2016. A control dataset included HES admission data for all other residents of the catchment area, without dementia diagnosis. These data only include people with ≥ 1 admission, so we used the 2011 national

census data [30] on over-65s in the catchment area to ascertain the denominator population.

Covariates

We extracted data from CRIS on age, sex, ethnicity, marital status, and socioeconomic status estimated using the Index of Multiple Deprivation (IMD) [31]; a higher score indicates more socioeconomic deprivation. We extracted dementia sub-type at last recording (grouped as Alzheimer's, vascular, Lewy body, other or unspecified (where aetiology unrecorded).) We estimated dementia severity using Mini Mental State Examination (MMSE) [32] scores (from structured and unstructured fields). For other aspects of clinical presentation, we used the Health of the Nation Outcome Scales (HoNoS), a 12-domain clinician-rated instrument completed at first assessment. It comprises subscales rated 0 (no problem) to 4 (severe/very severe problem) and has acceptable/good psychometric properties [33]. We dichotomised scores: 0 and 1 were grouped as no/minor problems, scores of ≥ 2 represented clinically significant problems. We used eight HoNOS domains of interest, rating problems with: agitation, self-injury, substance use, physical illness, hallucinations, depressed mood, activities of daily living, or living conditions. All covariates were taken from the recording closest to dementia diagnosis, except for dementia subtype, for which we used the last recording.

Statistical analysis

We first described the characteristics of our sample and then compared these according to hospitalisation during the study window.

Cumulative incidence and admission rate of hospitalisation

We calculated the cumulative incidence of hospitalisation (= number of people admitted at least once during study window/total number in the cohort) and the admission rate (= all admissions/person-years (PY), calculated as time between CRIS dementia diagnosis, and death or end of study window), with 95% confidence intervals [34]. We examined these outcomes for all admissions, then those coded as emergency and elective, during the first year following diagnosis and all follow-up. We then determined the distribution of the count of hospitalisation.

Age-standardised admission ratio for dementia

We calculated the age-standardised admission ratio for emergency and elective admissions (ratio of observed admissions for people with dementia to the expected admissions based on the control population, standardised to the control age distribution) [34]. We examined admissions during 2011, as the control denominator population was taken from the 2011 census. We used 5 year age bands for standardisation and calculated the control population by excluding people with dementia diagnosed between 2008 and 2016 from the control dataset and subtracting these from the denominator population.

Association of sociodemographic and clinical factors with hospitalisation

We used negative binomial regression to analyse associations of sociodemographic and clinical factors with the number of emergency and elective hospitalisations. We included in our multivariable analysis age, sex, marital status, ethnicity, IMD, MMSE, dementia subtype, HoNOS domains and year of diagnosis as a categorical variable, and in a separate analysis, as an ordinal variable. We included time of follow-up in our model as an exposure variable.

Our primary analyses examined predictors of admissions during the first year after diagnosis, as covariates were taken from time closest to diagnosis so held more salience for proximal admissions. We also judged that assessing admission rates by year of diagnosis would be biased if we used the full study period as, despite adjusting for years of follow up, those with longer duration of follow-up would be older when studied which could affect admission risk. In sensitivity analyses, we analysed predictors of hospital admissions throughout the full study period.

As 22% of the cohort had missing data on at least one predictor, we also conducted sensitivity analyses using multiple imputation by chained equations [35] for missing covariates to maximise statistical power. We used the *mi* package in STATA to create five imputed datasets constructed from all potential covariate and outcome variables, before using negative binomial regression on each imputed dataset and Rubin's rules [36] to combine coefficients.

We considered whether admission rates may be affected by more physically unwell people being diagnosed by the increasingly common liaison/consultation psychiatry services [37]. We therefore conducted post hoc sensitivity analyses of admission cumulative incidence and rate and the association of number of admission with year of diagnosis, while excluding people whose diagnosis was within 1 month of consultation psychiatry assessment.

Results

We obtained data on 10,137 eligible adults with dementia aged ≥ 65 years. The characteristics of the sample at dementia diagnosis are summarised in Table 1. The mean age of

Table 1 Socio-demographic and clinical characteristics of all people with dementia, and according to whether admitted to general hospital during follow-up

Characteristic		All people with dementia (n = 10,137)		Admitted to hospital (n = 7693)		Not admitted to hospital (n = 2444)		Significance test[a]
		n	%	n	%	n	%	
Age at diagnosis	Mean (SD)	82.1 (7.2)		82.1 (7.0)		81.8 (7.7)		$t = -2.3$, $p = 0.02$
	65–69	600	5.9	412	5.4	188	7.7	$\chi^2 = 47.4$, $p < 0.001$
	70–74	1203	11.9	866	11.3	337	13.8	
	75–79	1998	19.7	1541	20.0	457	18.7	
	80–84	2602	25.7	2044	26.6	558	22.8	
	85–89	2446	24.1	1890	24.6	556	22.8	
	90 +	1288	12.7	940	12.2	348	14.2	
	Missing	0		0		0		
Sex	Female	6262	61.8	4662	60.6	1600	65.5	$\chi^2 = 18.5$, $p < 0.001$
	Missing	1		1		0		
Ethnicity	White	7640	77.3	5915	78.4	1725	73.8	$\chi^2 = 28.9$, $p < 0.001$
	Asian	453	4.6	345	4.6	108	4.6	
	African/Caribbean	1445	14.6	1050	13.9	395	16.9	
	Other	344	3.5	234	3.1	110	4.7	
	Missing	255		149		106		
Marital status[b]	Married	3202	33.5	2454	33.5	748	33.4	$\chi^2 = 4.5$, $p = 0.21$
	Divorced	769	8.0	590	8.1	179	8.0	
	Widowed	3892	40.7	3007	41.1	885	39.5	
	Single	1701	17.8	1270	17.4	431	19.2	
	Missing	573		372		201		
Mean deprivation score[b] (SD)		27. 2 (11.1)		27.3 (11.1)		26.7 (11.1)		$t = -2.14$, $p = 0.03$
	Missing	40		22		18		
Mean MMSE[b] (SD)		18.6 (6.3)		18.6 (6.2)		18.6 (6.5)		$t = -0.17$, $p = 0.87$
	Missing	1579		1049		530		
Problem[b] with: (from HoNOS subscale)	Agitation	1998	20.7	1494	20.2	504	22.2	$\chi^2 = 4.3$, $p = 0.04$
	Self-injury	136	1.4	108	1.5	28	1.2	$\chi^2 = 0.65$, $p = 0.42$
	Alcohol/drugs	302	3.1	233	3.2	69	3.0	$\chi^2 = 0.07$, $p = 0.79$
	Physical illness	5511	57.1	4307	58.3	1204	53.1	$\chi^2 = 18.9$, $p < 0.001$
	Hallucinations	1354	14.1	1058	14.4	296	13.1	$\chi^2 = 2.2$, $p = 0.14$
	Depressed mood	1416	14.7	1083	14.7	333	14.7	$\chi^2 = 0.002$, $p = 0.96$
	Daily living	5981	62.1	4601	62.5	1380	61.0	$\chi^2 = 1.75$, $p = 0.19$
	Living conditions	1220	12.8	952	13.1	268	11.9	$\chi^2 = 1.9$, $p = 0.17$
	Missing[c]	513		452		315		
Last recorded dementia diagnosis	Alzheimer's disease	5166	51.0	3884	50.5	1282	52.5	$\chi^2 = 13.8$, $p = 0.008$
	Vascular dementia	2223	21.9	1741	22.6	482	19.7	
	Lewy body dementia	299	2.9	237	3.1	62	2.5	
	Other dementia	691	6.8	529	6.9	162	6.6	
	Unspecified dementia	1758	17.3	1302	16.9	456	18.7	
Year of diagnosis	2008	1215		1015	83.5	200	16.5	$\chi^2 = 371.8$, $p < 0.001$
	2009	1177		970	82.4	207	17.6	
	2010	1346		1094	81.3	252	18.7	
	2011	1445		1162	80.4	283	19.6	
	2012	1476		1131	76.6	345	23.4	
	2013	1545		1153	74.6	392	25.4	
	2014	1515		944	62.3	571	37.7	
	2015	418		224	53.6	194	46.4	

HoNOS health of the Nation Outcome Scale, *MMSE* mini-mental state examination

[a]Chi square test used to compare characteristics between admitted and non-admitted groups for categorical variables and t test used for continuous variables

[b]Based on clinical assessment nearest to first dementia diagnosis

[c]Figure for missing HoNOS score is for the HoNOS domain with most missing information

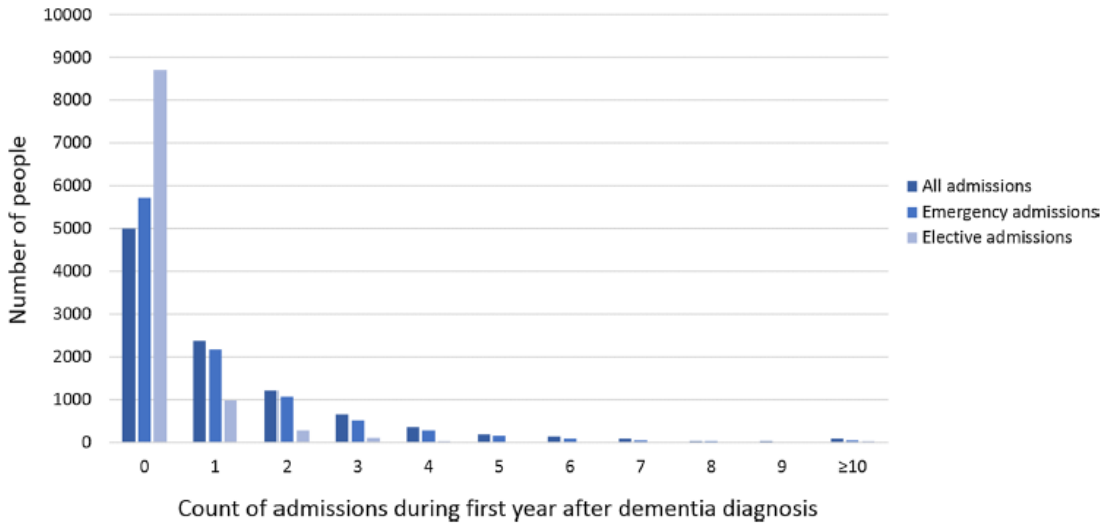

Fig. 1 Distribution of count of general hospital admissions for people with dementia during first year after diagnosis (n = 10,137)

people was 82.1 (standard deviation (SD) 7.2) years. The majority were female and white, with African/Caribbean forming the largest minority ethnic group. Mean MMSE score was 18.6 (SD 6.3) and around half of the cohort had Alzheimer's disease.

Cumulative incidence and admission rate of hospitalisation

During the first year following dementia diagnosis, 5127 [50.6% (95% CI 49.6, 51.6)] were admitted to hospital. The hospitalisation rate during the first year after diagnosis was 1.05/PY (1.03, 1.07) for emergency admissions and 0.44/PY (0.43, 0.46) for elective admissions. hospitalisation count distribution are shown in Fig. 1 (full data in eTable 2); 2245 people (22.2%) had ≥ 2 and 41 (0.4%) of the sample had ≥ 10 emergency hospitalisations during the year after diagnosis.

During the study window (median 2.5 years; interquartile range 1.3, 4.1; maximum 8.2 years), 7693 [75.9% (75.0, 76.7)] (Table 2) were hospitalized. During 28,425.3 PY total follow-up, the cohort experienced 35,716 general hospital admissions, of which 25,634 (71.8%) were emergency. The hospitalisation rate was 1.26/PY (1.24, 1.27), of which 0.90/PY (0.89, 0.91) were emergency, and 0.35/PY (0.35, 0.36) were elective.

In our sensitivity analysis excluding 1293 people whose dementia diagnosis was within 1 month of consultation psychiatry assessment, 76.1% (75.2, 77.0) of the remaining 8844 were admitted during the study window; hospitalisation rate = 1.13/PY (1.12, 1.14), of which 0.86 (0.84, 0.87) were emergency.

Table 2 Rate of general hospital admissions of people with dementia 2008–2016

Number of people ever admitted	7693/10,137
Cumulative incidence of any admission (%) (95% confidence interval)	75.9 (75.0, 76.7)
Person years[a]	28,425.3
Total number of all admissions	35,716
Admission rate (/PY) (95% confidence interval)	1.26 (1.24,1.27)
Number of emergency[b] admissions	25,634
Emergency admission rate (/PY)	0.90 (0.89, 0.91)
Number of elective[b] admissions	10,082
Elective admission rate (/PY) (95% confidence interval)	0.35 (0.35, 0.36)

PY person years

[a]PY calculated based on time between initial dementia diagnosis AND death OR end of window (whichever was earliest)

[b]Elective/emergency admission status according to admission record coding

Age-standardised admission ratio for dementia

The control group consisted of 105,889 residents without dementia diagnosis from SLaM, who had 31,233 emergency admissions and 62,796 elective admissions during 2011 (Table 3). The age-standardised admission ratio for people with dementia compared to those without was 2.06 (1.95, 2.18) for emergency admissions and 1.00 (0.93, 1.07) for elective admissions.

Table 3 Standardised admission ratio for people with dementia compared to those without diagnosed dementia, during 2011

	Age-groups	People without dementia			People with dementia			Expected number of admissions	
		n	Number of admissions	Admission rate (/yr)	n	Number of admissions	Admission rate (/yr)		
Emergency admissions	65–69	32,441	5146	0.16	76	81	1.07	12.1	Standardised emergency admission ratio (= observed/expected × 100)
	70–74	27,148	5962	0.22	186	145	0.78	40.8	
	75–79	20,744	6199	0.30	300	254	0.85	89.7	
	80–84	14,178	6209	0.44	380	324	0.85	166.4	
	85–89	7591	4649	0.61	331	340	1.03	202.7	
	90+	3787	3068	0.81	172	199	1.16	139.3	
	Total	105,889	31,233		1445	1343		651	2.06 (1.95, 2.18)
Elective admissions	65–69	32,441	16,938	0.52	76	41	0.54	39.7	Standardised elective admission ratio (= observed/expected × 100)
	70–74	27,148	16,772	0.62	186	206	1.11	114.9	
	75–79	20,744	14,622	0.70	300	305	1.02	211.5	
	80–84	14,178	9931	0.70	380	189	0.50	266.2	
	85–89	7591	3668	0.48	331	62	0.19	159.9	
	90+	3787	865	0.23	172	25	0.15	39.3	
	Total	105,889	62,796		1445	828		831	1.00 (0.93, 1.07)

Association of sociodemographic and clinical factors with hospitalisation

Emergency hospitalisation

Emergency hospitalisation rate within the first year after diagnosis (Table 4) was higher in fully-adjusted models for those who were older, from a more socio-economically deprived area, rated as having problem with physical illness, depressed mood, activities of daily living, or their living conditions, and those with non-Alzheimer's dementias. Women and people from minority ethnic groups had lower emergency hospitalisation rates.

Hospitalisation rates increased over time; IRR for people diagnosed in 2015, compared to 2008 = 1.39 (1.12, 1.73). Applying year of diagnosis as an ordinal independent variable, the IRR for each year increment was 1.03 (1.01, 1.05).

In sensitivity analyses, results were similar when we analysed the full study period (*eTable 3*) except that the association with year of diagnosis was attenuated. We found similar results when using multiple imputation for missing covariates (*eTable 4*). Excluding people diagnosed during consultation psychiatry assessment did not change our results.

Elective hospitalisation

Elective hospitalisation rates (Table 4) were higher for those who were younger, African/Caribbean ethnicity, from less socio-economically deprived areas, and those who had better cognition, problem with physical illness, activities of daily living and non-Alzheimer's dementias. Women and those with depressed mood at diagnosis had lower Hospitalisation rates. Elective admission rates did not change during the study period. Results were consistent in our sensitivity analyses (appendices 2,3).

Discussion

In a large secondary care cohort, we found high and increasing rates of emergency hospitalisation for people with dementia. Half of people with dementia were admitted to hospital in the year after diagnosis, three quarters were admitted during 2.5 years median follow-up, and multiple admissions were common. The emergency admission rate was 0.90 per person year and people with dementia had 2.1 times more emergency admissions than age-matched controls without diagnosed dementia; elective admissions did not differ between people with dementia and those without. Emergency but not elective hospitalisation rates increased since 2008. We found higher emergency hospitalisation rates in people who were older, male, white, more socio-economically deprived people and those with non-Alzheimer's dementia, worse activities of daily living and problems with their living conditions, and physical illness or depressed mood at diagnosis. A different pattern of predictors was found for elective admissions which were more frequent with younger age, African/Caribbean ethnicity, less socio-economic deprivation and milder dementia.

The hospitalisation rate in our study is higher than that reported in any previous study. Specifically, US research

Table 4 Predictors of general hospital admissions during first year after dementia diagnosis; multivariable negative binomial regression (n = 7863 with complete covariate data)

Characteristic		Emergency hospital admissions		Elective hospital admissions	
		IRR (95% CI)	*p* value	IRR (95% CI)	*p* value
Age (per 1 year increment)		**1.03 (1.02, 1.03)**	**< 0.001**	**0.96 (0.95, 0.98)**	**< 0.001**
Sex	Female	**0.77 (0.71, 0.84)**	**< 0.001**	**0.58 (0.49, 0.70)**	**< 0.001**
Ethnicity	White (Ref.)	1		1	
	Asian	**0.79 (0.66, 0.96)**	**0.02**	1.23 (0.85, 1.77)	0.27
	African/Caribbean	**0.80 (0.72, 0.90)**	**< 0.001**	**1.43 (1.13, 1.81)**	**0003**
	Other	**0.69 (0.55, 0.87)**	**0.001**	1.24 (0.79, 1.94)	0.35
Marital status	Married (Ref.)	1		1	
	Divorced	1.13 (0.97, 1.30)	0.11	1.33 (0.98, 1.82)	0.07
	Widowed	1.10 (1.00, 1.21)	0.05	1.03 (0.84, 1.27)	0.79
	Single	1.10 (0.98, 1.23)	0.11	0.95 (0.75, 1.21)	0.68
Deprivation score (per 10-unit increase in deprivation)		**1.05 (1.01, 1.09)**	**0.006**	**0.92 (0.86, 0.99)**	**0.04**
MMSE (per 1 unit decrease)		1.01 (1.00, 1.01)	0.05	**0.95 (0.94, 0.97)**	**< 0.001**
Problem with (from HoNOS subscale)[a]:	Agitated behaviour	1.02 (0.92, 1.13)	0.72	0.93 (0.74, 1.17)	0.56
	Self-injury	1.24 (0.92, 1.68)	0.16	0.64 (0.30, 1.36)	0.24
	Problem-drink/drugs	1.12 (0.91, 1.38)	0.30	1.43 (0.92, 2.23)	0.11
	Physical illness	**1.73 (1.59, 1.88)**	**< 0.001**	**1.81 (1.51, 2.18)**	**< 0.001**
	Hallucinations	1.03 (0.92, 1.15)	0.56	0.84 (0.66, 1.06)	0.14
	Depressed mood	**1.14 (1.02, 1.26)**	**0.02**	**0.67 (0.53, 0.85)**	**0.001**
	Daily living	**1.18 (1.08, 1.28)**	**< 0.001**	**1.33 (1.10, 1.62)**	**0.004**
	Living conditions	**1.16 (1.04, 1.30)**	**0.008**	0.82 (0.64, 1.05)	0.11
Last recorded dementia diagnosis	Alzheimer's disease (Ref.)	1		1	
	Vascular dementia	**1.41 (1.28, 1.55)**	**< 0.001**	**2.18 (1.75, 2.72)**	**< 0.001**
	Lewy body dementia	1.18 (0.95, 1.47)	0.13	1.46 (0.93, 2.29)	0.10
	Other dementia	1.08 (0.93, 1.25)	0.33	1.17 (0.84, 1.62)	0.35
	Unspecified dementia	**1.55 (1.40, 1.73)**	**< 0.001**	**1.43 (1.11, 1.83)**	**0.005**
Year of diagnosis (per 1 year later)	2008 (Ref.)	1		1	
	2009	**1.18 (1.01, 1.38)**		0.99 (0.71, 1.39)	
	2010	**1.26 (1.08, 1.47)**		1.37 (0.99, 1.90)	
	2011	**1.21 (1.04, 1.41)**		**1.78 (1.30, 2.43)**	
	2012	**1.32 (1.14, 1.53)**		**1.54 (1.13, 2.11)**	
	2013	**1.28 (1.10, 1.48)**		**1.50 (1.09, 2.06)**	
	2014	**1.29 (1.11, 1.50)**		1.34 (0.97, 1.84)	
	2015	**1.39 (1.12, 1.73)**		0.91 (0.56, 1.47)	
	Per one year later	**1.03 (1.01, 1.05)**	**0.001**	1.04 (1.00, 1.08)	0.07

CI confidence Interval, *HoNOS* health of the nation outcome scales, *IRR* incidence rate ratio, *MMSE* mini-mental state examination

Bold figures indicate $p < 0.05$ in multivariable analysis

[a]HoNOS subscale, dichotomised to 0–1 (no or minor problem) and 2–4 (problem behaviour)

cohorts have reported rates of only 0.16/PY admissions between 1991 and 2006 [17] and 0.42/PY admissions during 1994–2007 [16], and a French cohort had 0.22/PY admissions during 2000–2004 [14]. This study's proportion admitted during 1 year (56%) is also higher than any other study reporting this outcome, whose estimates were between 24 and 41% [7, 13, 19, 20, 38]. Admission rates for people with dementia compared to those without was higher in our study than in three of the four previous US studies examining this [7, 16, 21]. Direct comparison of admissions between countries is difficult because healthcare service organisation differ, but admission rates for the general populations of the UK and US have been reported as similar [39].

The higher rate in our study is partly due to our sample being derived from a clinical sample in which no-one with dementia was excluded and our use of national hospital records ensuring that almost complete outcome data—1% of UK hospital services are non-NHS [40] and this figure

would be lower for emergency admission of people with dementia—compared to population-based cohorts prone to 'healthy volunteer' selection bias [11] and selective attrition of more unwell participants [12]. Our cohort was also older at baseline (mean 82 years) than those in the other studies (mean 76–78 years). Furthermore, our study uses more recent data than any other study—we found increasing admissions from 2008 to 2016, so recent data would show higher hospitalisation rates. Increasing UK hospitalisation rates for older people generally have been reported by the Kings Fund [41], due to greater multi-morbidity related to longevity [42], lower tolerance of risk by public and professionals [43], and reduced availability of community services. Dementia diagnosis in community settings [44] and hospitals [45] has increased over the past decade and the 2012 UK policy of seeking possible dementia cases in elderly hospital inpatients [46] and referring to memory services for diagnosis may have resulted in more physically unwell people being diagnosed in the later years of our study, though our findings were adjusted for physical illness severity. While excluding people diagnosed by consultation psychiatry gave slightly lower admission rates, the role of these services did not explain changing admission rates over time.

We found as expected that having comorbid physical illness at diagnosis was the strongest predictor of subsequent emergency and elective hospitalisation. Previous studies have indicated that more severe dementia is associated with higher admission rates [15] and we found that functional impairment, rather than cognitive impairment, is independently associated with emergency and elective admission, consistent with two previous studies [13, 14]. Our findings that men [17, 47], lower socio-economic groups [13], non-Alzheimer's dementias [16, 19], and depression [14, 18] are associated with emergency admission are also consistent with previous studies. This research, from a more ethnically diverse area than previous studies, adds that non-White ethnic groups have fewer emergency admissions, possibly a result of greater family care [48]. We also found that problematic living conditions, reflecting whether home support is sufficient to meet basic necessities of light, heat and hygiene [49], was associated with emergency hospitalisation. This finding and the association with ethnicity and socio-economic status suggests that social factors are important predictors of admission risk. Declining UK social care spending since 2010 has been reported despite increasing numbers of older people [50] and UK social care has recently been described as 'struggling to meet the needs of older people' [51]. Our findings support the impression that social care pressures have resulted in insufficient home care and increasing hospitalisations.

We identified a different pattern of predictors for elective hospitalisations. Younger and less cognitively impaired people had higher rates of elective admission, suggesting that planned treatment is preferentially delivered to those with less advanced dementia. Less socio-economically deprived people had more elective admissions, which may reflect more healthcare engagement in these groups or bias in clinician decision making [52]. African/Caribbean people had higher admission rates, which may be due to higher rates of elective renal dialysis [53], which have been found to be 1.88 times higher in the black UK population compared to white ethnic groups [54].

Limitations

Our study has potential limitations. Analyses of hospitalisation predictors were limited to those recorded during routine practice and data on physical comorbidity were limited; we used the HoNOS physical illness domain in our analyses which has been reported to have acceptable psychometric properties [33] and its strong association with admission in our study supports its predictive validity. However, future studies using high quality data on premorbid illness should consider which conditions are associated with hospitalisation in order to identify specific targets for preventative medical treatment. We did not have data on other potentially important factors, such as influenza or pneumococcal vaccination status or residential setting. One study found that admission rates of nursing home residents were one quarter that of the community-dwelling population with dementia [55], suggesting that care home residence may protect against hospitalisation in people with severe dementia. However, our analysis studied admission during the first year after diagnosis, so the proportion of patients living in nursing homes is likely to be considerably lower than the overall UK figure of 16% of people with dementia estimated to live in nursing homes [56].

CRIS only contains records of people with dementia who have consulted secondary healthcare services so our results may not generalise to those with undiagnosed dementia. Diagnosis of dementia may indicate those with more active health-seeking behaviours, possibly including hospitalisation, thereby overestimating hospitalisation rate of all people with dementia whether diagnosed or undiagnosed. However, a recent systematic review found no correlation between care-seeking behaviours and hospitalisation rate [57], so care seeking behaviour is unlikely to affect the generalisability of our results.

Our study may also not generalise to those whose dementia was diagnosed in primary care or geriatric medicine settings, which is the norm in some areas of the UK [58]. However, this is relatively rare in the studied catchment area, where the custom is to refer to memory services as these are the mainstay of UK dementia diagnostic practice. This secondary mental healthcare service also provides some post-diagnostic care, so individuals diagnosed in other services

may have subsequently received CRIS diagnosis. In our previous study, *92% of people with dementia recorded in hospital records had previously been seen by the mental health services and given a diagnosis of dementia in CRIS* [45]. We therefore judge our study sample to encompass and closely resemble most of those with diagnosed dementia in the large inner-city and suburban catchment area. In addition, our analyses use data from a single mental healthcare provider whose services may differ from other providers, so the analysed sample may not generalise nationally. However the estimated proportion of people with dementia living in the catchment area who have been diagnosed is relatively high at 75.2%, compared to 67.6% nationally [59]. Finally, some of the control population in our analysis may have had undiagnosed dementia, which would mean that our study underestimates the standardised admission ratio as people with undiagnosed dementia may have more admissions than those without dementia.

Conclusions

The current study provides evidence for high and rising emergency hospitalisation rates of people with dementia. Hospital admission of people with dementia can be harmful and costly and, while we recognise that many admissions are appropriate, the potentially modifiable factors associated with admission in this study suggest that many are, in all probability, avoidable such as by improving quality of living conditions and maximising functional ability. Developing effective interventions to reduce avoidable admissions of community-dwelling people with dementia is a major priority; a recent systematic review found no effective interventions [60] although there has been success in those without dementia [61]. Understanding the causes of admissions informs the development of strategies to reduce admission, allowing future evaluation in trials. That admission rates are rising could indicate that cross-specialty health and social care is currently not meeting the needs of people with dementia and their carers [50, 51]. Reducing expensive, potentially harmful hospitalisation can only be done by improving alternatives in the community.

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Authors' contribution AS conceived the idea for this study, designed the analysis plan, conducted the data analysis, interpreted the data and drafted the manuscript and figures. GP conducted the data analysis, interpreted the data and revised the manuscript for important intellectual content. CM interpreted the data and revised the manuscript for important intellectual content. AS-M interpreted the data and revised the manuscript for important intellectual content. G Lewis conceived the idea for this study, designed the analysis plan, interpreted the data and revised the manuscript for important intellectual content. RS conceived the idea for this study, designed the analysis plan, interpreted the data and revised the manuscript for important intellectual content. G Livingston conceived the idea for this study, designed the analysis plan, interpreted the data and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: AS reports funded a grant from the Wellcome trust, G Lewis reports a grant from University College London and G Livingston reports grants from Department of Health, National Institute for Health Research (Health Technology Assessment, Biomedical Research Centre, Efficacy and Mechanism Evaluation streams), Alzheimer society and the Economic and Social Research Council during the conduct of the study. RS reports grants from Janssen, Roche, and other financial relationships with GlaxoSmithKline outside the submitted work. No other relationships or activities that could appear to have influenced the submitted work.

Ethical approval The Oxfordshire Research Ethics Committee C (reference 08/H0606/71 + 5) approved the mental health care records data resource (CRIS) for secondary analysis, including linked hospitalization data (HES). The terms of the ethical approval do not require consent to be provided but all participants have the right to opt out of data use at any time.

References

1. Langa KM, Larson EB, Crimmins EM, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. JAMA Intern Med. 2017;177(1):51–8.
2. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, et al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. BMJ. 2017;358:j2856.
3. Sampson EL, White N, Leurent B, et al. Behavioural and psychiatric symptoms in people with dementia admitted to the

acute hospital: prospective cohort study. Br J Psychiatry. 2014;205(3):189–96.
4. Clerencia-Sierra M, Calderon-Larranaga A, Martinez-Velilla N, et al. Multimorbidity patterns in hospitalized older patients: associations among chronic diseases and geriatric syndromes. PLoS ONE. 2015;10(7):e0132909.
5. Livingston G, Leavey G, Manela M, et al. Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. BMJ. 2010;341:c4184.
6. White N, Leurent B, Lord K, Scott S, Jones L, Sampson EL. The management of behavioural and psychological symptoms of dementia in the acute general medical hospital: a longitudinal cohort study. Int J Geriatr Psychiatry. 2017;32(3):297–305.
7. Zhao Y, Kuo TC, Weir S, Kramer MS, Ash AS. Healthcare costs and utilization for medicare beneficiaries with Alzheimer's. BMC Health Serv Res. 2008;8:108.
8. Zhu CW, Cosentino S, Ornstein K, Gu Y, Andrews H, Stern Y. Use and cost of hospitalization in dementia: longitudinal results from a community-based study. Int J Geriatr Psychiatry. 2015;30(8):833–41.
9. Sager MA, Rudberg MA, Jalaluddin M, et al. Hospital admission risk profile (HARP): identifying older patients at risk for functional decline following acute medical illness and hospitalization. J Am Geriatr Soc. 1996;44(3):251–7.
10. Bynum JP, Rabins PV, Weller W, Niefeld M, Anderson GF, Wu AW. The relationship between a dementia diagnosis, chronic illness, medicare expenditures, and hospital use. J Am Geriatr Soc. 2004;52(2):187–94.
11. Fry A, Littlejohns T, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with the general population. Am J epidemiol. 2017;186(9):1026–34.
12. Brilleman SL, Pachana NA, Dobson AJ. The impact of attrition on the representativeness of cohort studies of older people. BMC Med Res Methodol. 2010;10(1):71.
13. Andrieu S, Reynish E, Nourhashemi F, et al. Predictive factors of acute hospitalization in 134 patients with Alzheimer's disease: a one year prospective study. Int J Geriatr Psychiatry. 2002;17(5):422–6.
14. Voisin T, Andrieu S, Cantet C, Vellas B, Group RF. Predictive factors of hospitalizations in Alzheimer's disease: a two-year prospective study in 686 patients of the REAL FR study. J Nutr Health Aging. 2010;14(4):288–91.
15. Albert SM, Costa R, Merchant C, Small S, Jenders RA, Stern Y. Hospitalization and Alzheimer's disease: results from a community-based study. J Gerontol Ser A Biol Sci Med Sci. 1999;54(5):M267–71.
16. Phelan EA, Borson S, Grothaus L, Balch S, Larson EB. Association of incident dementia with hospitalizations. JAMA. 2012;307(2):165–72.
17. Rudolph JL, Zanin NM, Jones RN, et al. Hospitalization in community-dwelling persons with Alzheimer's disease: frequency and causes. J Am Geriatr Soc. 2010;58(8):1542–8.
18. Russ TC, Parra MA, Lim AE, Law E, Connelly PJ, Starr JM. Prediction of general hospital admission in people with dementia: cohort study. Br J Psychiatry. 2015;206(2):153–9.
19. Landi F, Gambassi G, Lapane KL, Sgadari A, Mor V, Bernabei R. Impact of the type and severity of dementia on hospitalization and survival of the elderly. The SAGE study group. Dement Geriatr Cogn Disord. 1999;10(2):121–9.
20. Tuppin P, Kusnik-Joinville O, Weill A, Ricordeau P, Allemand H. Primary health care use and reasons for hospital admissions in dementia patients in France: database study for 2007. Dement Geriatr Cogn Disord. 2009;28(3):225–32.
21. Malone DC, McLaughlin TP, Wahl PM, et al. Burden of Alzheimer's disease and association with negative health outcomes. Am J Manag Care. 2009;15(8):481–8.
22. Department of Health. Living well with dementia: a national dementia strategy. London: HMO Stationery Office; 2009.
23. National Collaborating Centre for Mental Health. Dementia: a NICE-SCIE guideline on supporting people with dementia and their carers in health and social care. London: British Psychological Society; 2007.
24. Perera G, Broadbent M, Callard F, et al. Cohort profile of the South London and Maudsley NHS foundation trust biomedical research centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open. 2016;6(3):e008721.
25. Burns A, WIlkinson A, Peachey S. Best practice in memory services: learning from across England. London: NHS England; 2014.
26. Jackson RG, Patel R, Jayatilleke N, et al. Natural language processing to extract symptoms of severe mental illness from clinical text: the clinical record interactive search comprehensive data extraction (CRIS-CODE) project. BMJ Open. 2017;7(1):e012012.
27. Cunningham H. GATE, a general architecture for text engineering. Comput Humanit. 2002;36(2):223–54.
28. Health and social care information centre. *HES* data dictionary: admitted patient care. London: NHS Digital; 2017.
29. World Health Organization. *International statistical classification of diseases and health related problems (The) ICD-10*, World Health Organization; 2004.
30. Office for National Statistics, National Records of Scotland, Northern Ireland Statistics and Research Agency. *2011 Census aggregate data.* Vol (Edition: June 2016): UK Data Service; 2016.
31. Department for Communities and Local Government. English indices of deprivation 2015. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015. Accessed 30 Mar 2017.
32. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
33. Pirkis JE, Burgess PM, Kirk PK, Dodson S, Coombs TJ, Williamson MK. A review of the psychometric properties of the Health of the nation outcome scales (HoNOS) family of measures. Health Qual Life Outcomes. 2005;3(1):76.
34. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2008.
35. Oudshoorn CGM, Buuren S, Rijckevorsel JLA. Flexible multiple imputation by chained equations of the AVO-95 survey. Leiden: TNO Prevention and Health; 1999.
36. Rubin DB. Multiple imputation for nonresponse in surveys. New Jersey: Wiley; 2004.
37. NHS England. Achieving better access to mental health services by 2020. Periodical. 2014.
38. Mayeda ER, Whitmer RA, Glymour MM, Quesenberry CP. Race/ethnic differences in hospitalization and emergency room visits after diagnosis of dementia. Alzheimer's Dement. 2016;12(7 Supplement):P700–1.
39. Squires DA. The US health system in perspective: a comparison of twelve industrialized nations. Issue Br (Commonwealth Fund). 2011;16:1–14.
40. National Audit Office. Healthcare across the UK: a comparison of the NHS in England, Scotland, Wales and Northern Ireland. In: The Stationery Office London; 2012
41. Imison C, Poteliakhoff E, Thompson J. Older people and emergency bed use: exploring variation. King's Fund; 2012.
42. Jagger C, Matthews FE, Wohland P, et al. A comparison of health expectancies over two decades in England: results of the cognitive function and ageing study I and II. Lancet. 2016;387(10020):779–86.

43. Wittenberg R, Sharpin L, McCormick B, Hurst J. Understanding emergency hospital admission of older people. Oxford: Centre for Health Service Economics & Organisation; 2014.
44. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. Lancet Public Health. 2017;2(3):e149–56.
45. Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of general hospital dementia diagnoses in England: sensitivity, specificity, and predictors of diagnostic accuracy 2008–2016. *Alzheimer's Dement*. 2018;14(7):933–43.
46. Department of Health. Using the Commissioning for Quality and Innovation (CQUIN) payment framework Guidance on new national goals for 2012-13. In: Department of Health; 2012.
47. Knapp M, Chua KC, Broadbent M, et al. Predictors of care home and hospital admissions and their costs for older people with Alzheimer's disease: findings from a large London case register. BMJ Open. 2016;6(11):e013591.
48. Mukadam N, Cooper C, Livingston G. A systematic review of ethnicity and pathways to care in dementia. Int J Geriatr Psychiatry. 2011;26(1):12–20.
49. Wing J, Curtis R, Beevor A. Health of the nation outcome scales (HoNOS): glossary for HoNOS score sheet. Br J Psychiatry. 1999;174(5):432–4.
50. Age UK. Briefing: Health and Care of Older People in England (2017). 2017.
51. Humphries R, Hall P, Charles A, Thorlby R, Holder H. Social care for older people: Home Truths. The King's Fund; 2016.
52. Haider AH, Schneider EB, Sriram N, et al. Unconscious race and social class bias among acute care surgical clinicians and clinical treatment decisions. JAMA surg. 2015;150(5):457–64.
53. C-y Hsu, Lin F, Vittinghoff E, Shlipak MG. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. J Am Soc Nephrol. 2003;14(11):2902–7.
54. Mathur R, Dreyer G, Yaqoob MM, Hull SA. Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study. BMJ Open. 2018;8(3):e020145.
55. Skoldunger A, Fastbom J, Wimo A, Fratiglioni L, Johnell K. Impact of inappropriate drug use on hospitalizations, mortality, and costs in older persons and persons with Dementia: findings from the SNAC Study. Drugs Aging. 2015;32(8):671–8.
56. Prince M, Knapp M, Guerchet M, et al. Dementia UK: update. London: Alzheimer's Society; 2014.
57. van Loenen T, van den Berg MJ, Faber MJ, Westert GP. Propensity to seek healthcare in different healthcare systems: analysis of patient data in 34 countries. BMC Health Serv Res. 2015;15(1):465.
58. Dodd E, Cheston R, Cullum S, et al. Primary care-led dementia diagnosis services in South Gloucestershire: themes from people and families living with dementia and health care professionals. Dementia. 2016;15(6):1586–604.
59. NHS England. Dementia diagnosis monthly workbook. 2017; https://www.england.nhs.uk/mental-health/dementia/monthly-workbook/. Accessed 30 Mar 2017.
60. Phelan EA, Debnam KJ, Anderson LA, Owens SB. A systematic review of intervention studies to prevent hospitalizations of community-dwelling older adults with dementia. Med Care. 2015;53(2):207.
61. Naylor MD, Brooten D, Campbell R, et al. Comprehensive discharge planning and home follow-up of hospitalized elders: a randomized clinical trial. JAMA. 1999;281(7):613–20.

Appendix 9: Association of baseline characteristics of Whitehall II participants and association with participation at successive age points

	50 years (n=8,853)		60 years (n=7,710)		70 years (n=5,137)	
Participated?	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
n	**8,853**	**1,455**	**7,710**	**2,598**	**5,137**	**5,171**
Mean baseline age	45.2	43.1	45.5	43.2	47.1	42.8
p value	< 0.001		< 0.001		<0.001	
% Male	67.3	64.2	68.6	61.8	69.8	64.0
p value	0.02		<0.001		<0.001	
% Married at baseline	74.7	70.5	75.9	68.6	77.7	70.5
p value	0.001		<0.001		<0.001	
Mean baseline social network score	7.0	6.8	7.0	6.7	7.0	6.9
p value	0.03		< 0.001		0.02	
% Dementia case	4.4	4.9	4.8	3.7	4.7	4.3
p value	0.44		0.02		0.28	

Appendix 10: Association of baseline characteristics of Whitehall II participants and association with missing social data at successive age points

	50 years (n=8,853)		60 years (n=7,710)		70 years (n=5,137)	
Complete data?	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
n	**8,622**	**231**	**7,476**	**234**	**4,950**	**187**
Mean baseline age	45.2	45.5	45.5	45.0	47.1	47.3
p value	0.43		0.20		0.52	
% Male	67.4	64.1	68.7	65.8	70.0	62.6
p value	0.28		0.35		0.03	
% Married at baseline	74.7	71.9	76.3	63.3	78.2	65.2
p value	0.32		< 0.001		< 0.001	
Mean baseline social network score	7.0	4.3	7.1	5.5	7.1	6.2
p value	< 0.001		< 0.001		< 0.001	
% Dementia case	4.3	9.5	4.7	6.8	4.6	7.5
p value	< 0.001		0.13		0.07	

Appendix 11: Association of characteristics of Whitehall II participants with missing cognitive data in successive study phases

Study phase	5 (n=7,780)		7 (n=6,967)		9 (n=6,761)		11 (n=6,308)		12 (n=5,631)		5-12 (n=8,355) [b]	
Complete data?	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
n	**5,882**	**1,988**	**5,984**	**653**	**6,009**	**752**	**5,486**	**822**	**4,734**	**897**	**7,551**	**804**
Mean baseline age	44.6	45.4	44.5	46.4	44.2	46.5	43.8	46.3	43.4	45.6	44.6	46.0
p value	< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	
% Male	71.3	64.3	71.4	59.4	72.1	57.1	72.5	58.9	73.6	61.1	70.3	59.3
p value	< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	
% Married at baseline	75.9	73.8	76.4	73.2	76.5	72.7	76.7	75.1	77.4	74.1	75.9	69.2
p value	0.07		0.07		0.02		0.29		0.04		< 0.001	
Mean social network score [a]	7.4	7.2	7.6	7.3	7.6	7.6	8.0	7.6	8.1	7.7	7.0	6.8
p value	0.04		0.12		0.88		0.002		0.001		0.04	
% Dementia case	3.8	6.3	3.8	7.5	2.8	7.4	1.8	6.8	0.9	4.5	4.0	7.8
p value	< 0.001		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001	

Notes: [a] Social network score taken from respective study phase, apart from phase 9 and 12, when social contact was not measured, when score from preceding study phase was used. [b] Column refers to participants who have provided cognitive function data at any point during study phases 5 to 12

Appendix 12: **Association between social network contact and subsequent incident dementia: Weighted and unweighted hazard ratio for dementia associated with higher levels of social network contact**

Age:			**50 years**	**60 years**	**70 years**
Mean years follow-up			**23.1 (6.2)**	**14.6 (6.9)**	**7.5 (4.4)**
n included			**8,487**	**7,439**	**4,888**
All social contact	**Weighted**	Per standard deviation increase in social contact	0.92 (0.83, 1.02)	**0.88 (0.79, 0.98)**	0.91 (0.78, 1.06)
	Unweighted		0.91 (0.82, 1.01)	**0.88 (0.79, 0.98)**	0.95 (0.83, 1.09)
n included			**8,643**	**7,617**	**5,035**
Friend contact	**Weighted**	Per standard deviation increase in social contact	0.96 (0.86, 1.07)	**0.90 (0.81, 1.00)**	0.91 (0.80, 1.05)
	Unweighted		0.96 (0.86, 1.06)	**0.90 (0.80, 1.00)**	0.93 (0.81, 1.06)
n included			**8,493**	**7,449**	**4,889**
Relative contact	**Weighted**	Per standard deviation increase in social contact	0.91 (0.82, 1.02)	0.92 (0.83, 1.03)	0.94 (0.80, 1.11)
	Unweighted		**0.89 (0.80, 0.99)**	0.92 (0.83, 1.03)	0.99 (0.86, 1.13)

Notes: Weighted using inverse probability weighting for inclusion in fully-adjusted model; all results adjusted for age, sex, education, social class, ethnicity, smoking, alcohol, exercise, employment status and marital status; Bold results indicate $p<0.05$; Social class based upon occupational grade

Appendix 13: Hazard ratio from Cox regression models for dementia according to all social contact without imputed phase 1 data

Age:		**50 years**	**60 years**
n included in fully adjusted model (weighted n)		**7,804 (9,827)**	**7,165 (9,456)**
All social contact	Per 1 SD increase	0.92 (0.82, 1.02)	**0.89 (0.80, 0.99)**
n included in fully adjusted model (weighted n)		**8,438 (9,838)**	**7,348 (9,726)**
Friend contact	Per 1 SD increase	0.94 (0.85, 1.05)	0.91 (0.81, 1.01)

Key: SD = standard deviation

Notes: All results adjusted for age, sex, education, grade, ethnicity, smoking, alcohol and exercise, employment and marital status Weighted according to inverse of probability of inclusion in fully adjusted model; Bold results indicate p<0.05; Continuous results give HR for 1 standard deviation increase in social network contact

Appendix 14: Association between social contact change from age 60 to 70 years and subsequent incident dementia during mean 7.5 years follow-up: weighted and unweighted adjusted hazard ratios for dementia associated with continuous and categorical measure of social contact

		All social contact	Friend contact	Relative contact
n included in fully adjusted model (weighted n)		**4,534 (8,398)**	**4,534 (8,132)**	**4,534 (8,401)**
Weighted	Per one-point increase in social contact score from age 60 to 70	1.00 (0.94, 1.06)	0.99 (0.91, 1.07)	1.01 (0.93, 1.10)
Unweighted		1.01 (0.96, 1.07)	1.00 (0.93, 1.08)	1.02 (0.95, 1.08)
Weighted	Remain high (ref)	1	1	1
	Remain medium	1.33 (0.81, 2.19)	1.12 (0.64, 1.96)	0.77 (0.44, 1.37)
	Remain low	1.18 (0.70, 1.99)	1.22 (0.71, 2.11)	1.12 (0.68, 1.85)
	Increasing	1.28 (0.80, 2.02)	1.38 (0.86, 2.20)	1.08 (0.70, 1.67)
	Decreasing	1.07 (0.63, 1.82)	1.15 (0.66, 2.00)	0.91 (0.58, 1.44)
Unweighted	Remain high (ref)	1	1	1
	Remain medium	1.32 (0.83, 2.10)	1.26 (0.76, 2.08)	0.73 (0.44, 1.20)
	Remain low	1.06 (0.66, 1.72)	1.33 (0.81, 2.18)	1.05 (0.68, 1.64)
	Increasing	1.22 (0.80, 1.88)	1.56 (1.02, 2.41)	1.06 (0.70, 1.60)
	Decreasing	0.99 (0.61, 1.60)	1.24 (0.86, 2.04)	0.90 (0.59, 1.37)

Notes: All results adjusted for age, sex, education, social class, ethnicity, smoking, alcohol, exercise, employment status and marital status and for continuous measure, additionally adjusted for social contact at 60 years. Weighted results are weighted for probability of inclusion in fully adjusted model. Remain high = high at 60 years and 70 years; remain medium = medium at 60 years and 70 years; remain low = low at 60 years and 70 years; increasing = change from low at 60 years to medium or high at 70 years or from medium at 60 years to high at 70 years; decreasing change from high at 60 years to medium or low at 70 years or from medium at 60 years to low at 70

Appendix 15: Differences in baseline cognition and cognitive change per 10 years between Whitehall II study participants with preceding medium and high social contact frequency, compared to those with low social contact

Social domain	Cognitive domain	Social contact tertile (reference group=low)	Fully-adjusted differences	
			Baseline cognition (standard deviations)	**Cognitive change** (standard deviations / 10y)
All social contact	Combined cognition	Medium	0.02 (-0.02, 0.06)	0.00 (-0.02, 0.02)
		High	**0.07 (0.03, 0.11)**	-0.01 (-0.03, 0.01)
	Verbal fluency	Medium	0.02 (-0.02, 0.07)	-0.00 (-0.03, 0.02)
		High	**0.08 (0.03, 0.12)**	-0.00 (-0.03, 0.02)
	Verbal memory	Medium	0.03 (-0.02, 0.08)	-0.00 (-0.03, 0.03)
		High	**0.05 (0.00, 0.10)**	-0.01 (-0.04, 0.02)
	Reasoning	Medium	-0.01 (-0.05, 0.03)	0.00 (-0.02, 0.02)
		High	**0.01 (-0.03, 0.05)**	-0.01 (-0.03, 0.01)
Friend contact	Combined cognition	Medium	0.01 (-0.04, 0.05)	-0.1 (-0.04, 0.00)
		High	**0.08 (0.03, 0.12)**	**-0.03 (-0.05, -0.00)**
	Verbal fluency	Medium	0.02 (-0.03, 0.07)	-0.02 (-0.04, 0.01)
		High	**0.10 (0.05, 0.15)**	-0.02 (-0.05, 0.00)
	Verbal memory	Medium	0.03 (-0.02, 0.08)	-0.01 (-0.04, 0.02)
		High	**0.04 (0.01, 0.09)**	-0.02 (-0.06, 0.01)
	Reasoning	Medium	0.02 (-0.03, 0.06)	0.00 (-0.02, 0.02)
		High	0.02 (-0.02, 0.06)	-0.01 (-0.03, 0.01)
Relative contact	Combined cognition	Medium	0.02 (-0.02, 0.06)	-0.00 (-0.02, 0.02)
		High	0.01 (-0.03, 0.06)	0.00 (-0.02, 0.03)
	Verbal fluency	Medium	0.01 (0.03, 0.06)	0.01 (-0.01, 0.03)
		High	0.02 (-0.03, 0.07)	0.00 (-0.03, 0.03)
	Verbal memory	Medium	0.03 (-0.01, 0.08)	-0.00 (-0.03, 0.03)
		High	-0.01 (-0.06, 0.05)	0.02 (-0.02, 0.05)
	Reasoning	Medium	-0.00 (-0.04, 0.04)	-0.01 (-0.02, 0.01)
		High	0.00 (-0.04, 0.05)	-0.00 (-0.03, 0.02)

Notes: Results adjusted for age, sex, education, social class, ethnicity, smoking, alcohol, exercise, employment status, and marital status at baseline; bold figures indicate $p < 0.05$

Appendix 16: Differences in baseline cognition and cognitive change per 10 years between Whitehall II participants with preceding high and low social contact frequency, according to whether subsequently developed dementia

Social domain	Cognitive domain	Dementia-free		Dementia cases	
		Baseline cognition (standard deviations)	**Cognitive change** (standard deviations / 10y)	**Baseline cognition** (standard deviations)	**Cognitive change** (standard deviations / 10y)
All social contact	Combined cognition	**0.06 (0.02, 0.10)**	-0.01 (-0.03, 0.00)	**0.42 (0.06, 0.75)**	-0.16 (-0.38, 0.06)
	Verbal fluency	**0.07 (0.03, 0.12)**	-0.01 (-0.03, 0.02)	0.22 (-0.10, 0.54)	-0.07 (-0.29, 0.14)
	Verbal memory	0.04 (-0.01, 0.09)	-0.01 (-0.04, 0.02)	**0.51 (0.14, 0.88)**	-0.20 (-0.46, 0.05)
	Reasoning	0.01 (-0.03, 0.05)	-0.01 (-0.03, 0.01)	0.09 (-0.20, 0.38)	0.00 (-0.21, 0.21)
Friend contact	Combined cognition	**0.08 (0.03, 0.12)**	**-0.03 (-0.05, -0.00)**	**0.35 (0.01, 0.69)**	**-0.28 (-0.50, -0.06)**
Relative contact	Combined cognition	-0.01 (-0.05, 0.04)	0.00 (-0.02, 0.03)	0.28 (-0.08, 0.63)	-0.03 (-0.26, 0.21)

Notes: Baseline cognition centred at age 56 years; Number included in analysis of dementia-free participants = 6,810, dementia-cases = 282; All figures adjusted for age, sex, education, social class, ethnicity, smoking, alcohol, exercise, employment status, and marital status at baseline; Bold figures indicate $p < 0.05$

Appendix 17: Number of predicted cases of dementia in Whitehall II study participants using prevalence data from Cognitive Function and Aging study

Age at end of follow-up (death or 31st March 2017)	n	Dementia prevalence in CFAS-II [a] (%)	n of expected dementia cases
≤69 years	2,687	1.2	32
70 – 74 years	2,693	3.0	81
75 – 79 years	2,065	5.2	107
≥ 80 years	2,863	10.6	303
Total	10,308		523

Notes: [a] data from (Matthews et al., 2013)